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PHYSICIANS' HALL, 14th April 1898

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A MANUAL OF

# GENERAL PATHOLOGY

A

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OF

# GENERAL PATHOLOGY

FOR

STUDENTS AND PRACTITIONERS

BY

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1898

"Nil tam difficile est quin quærendo investigari possit."

TO

JOSEPH, LORD LISTER,

WHOSE WORK ON ANTISEPTICS IS ONE OF THE GREATEST EVIDENCES
FOR THE PRACTICAL UTILITY OF A STUDY OF

GENERAL PATHOLOGY,

**This volume is respectfully dedicated**

BY

THE AUTHOR.

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# PREFACE.

By this work I have endeavoured to fill, in some degree, a lacuna in the modern literature of Pathology,—a literature which has of late years grown to such an extent that it is no longer possible adequately to treat General Pathology and Pathological Anatomy in a single text-book of moderate size.

For a variety of reasons, General or Experimental Pathology has always received scantier attention from teachers—and therefore from students—than Pathological Anatomy. This, I believe, is a serious mistake from the point of view of training students for the active practice of medicine. The practising physician or surgeon is required not only to observe facts, but also to draw conclusions from those facts; and just as a study of pathological anatomy is one of the best modes of training his powers of observation, so a study of general pathology is one of the best modes of educating his reasoning faculties.

Neither branch of the science, however, must exclude the other, for pathological anatomy alone would tend to convert the student into a storehouse of isolated facts, and general pathology alone would tend to convert him into a mere theorist. Hence though, in the present work, I have almost entirely omitted reference to details of pathological anatomy, this is to be ascribed, firstly, to the exigences of space, and, secondly, to the fact that text-books on pathological anatomy are both many and excellent. It must, on no account, be ascribed to a belief on my part that general pathology is the whole of pathology, even for teaching purposes.

The general arrangement of the book, and especially of Chapter XIII., has been a matter of serious consideration. I have, however, thought that the importance of teaching the interdependence of tissues outweighs the advantage of discussing individual subjects in separate chapters. I trust that the synopses and the full indexes will considerably reduce the disadvantage arising from the length of some of the chapters.

The discussion of lymph- and œdema-formation has naturally crept to some length. My regret on this score is lessened because the subject is, at the present time, the great battlefield of "vital" and "physical" theories, and is, therefore, of considerable interest apart from its intrinsic pathological importance.

With regard to the use of names of authors, I have also experienced difficulty. Complete omission of names, I believe, renders retention of facts and arguments in the memory as difficult as their excessive use. As my book is primarily intended for students, I have endeavoured to steer a middle course. Insertion of references to original papers at the end of the chapters has been restricted, in the main, to instances where the work is comparatively recent, or where the reference is not to be found in easily accessible books. Nevertheless, literature on any particular subject discussed in the text can generally be found with ease by referring to one of the papers I have cited.

My information has, for the most part, been derived directly from the original papers, but it is needless to say that Cohnheim's *Lectures on General Pathology* have been laid heavily under contribution. I cannot leave this part of the subject without expressing my great obligation to Professor Clifford Allbutt's *System of Medicine.* Though I had collected much of my literature before Professor Allbutt's volumes appeared, it was of the utmost advantage to me to read articles written by others, who not only had traversed the same ground, but also were authors of some of the most important investigations on the subjects they treated. My only regret is that no more than Vols. I.–IV. had appeared when my own work went to press. I have the greater pleasure in referring to the *System of Medicine*, because I am thereby, in so many instances, acknowledging my indebtedness to personal and valued friends.

The number of those who have actively helped me with advice and criticism is so great, that the limits of a preface do not allow me to name them individually. But I must make special mention of the late Professor Roy, whose teaching upon the Pathology of the Heart is the basis of my chapter on the subject; of Dr Howship Dickinson, whose help in connection with the subject of Orthopnœa has been especially valuable; of Professor Schäfer, who kindly placed at my disposal proofs of his *Text-Book of Physiology for Advanced Students*; of Dr Pembrey, who criticised and suggested many improvements in my chapter on the Pathology of Heat Regulation; of Dr Lorrain Smith, who showed me the same kindness with regard to the Pathology of Respiration. To one and all of these I tender my hearty thanks.

My indebtedness to Mr W. L. H. Duckworth, Fellow of Jesus College and Lecturer on Anthropology in the University of Cambridge, I cannot adequately express. Resolutely adopting the student's point of view, he has read through the entire work in proof, and, in several instances, has been able to point out ambiguities of expression that had escaped my notice.

W. S. L.-B.

LONDON, *March* 1898.

# GENERAL PATHOLOGY.

## CHAPTER I.

### INTRODUCTION.

PATHOLOGY is the science which treats of changes and processes in disease. It falls into at least two natural divisions: (1) that which deals with structure (Morbid Anatomy and Histology); (2) that which deals with function (Morbid Physiology, or General Pathology). For the body in disease must be studied from both of these aspects, just as the body in health.

Our knowledge of morbid anatomy is more advanced than our knowledge of morbid physiology, just as normal anatomy is more advanced than normal physiology. This must be so. For life and death do not make the same difference in the case of structure that they make in the case of function: the pancreas, for example, has much the same coarse anatomy whether living or dead, but with its death its physiology ceases. Function is bound up with life; and since life means incessant change, examination of function is difficult or impossible in many cases, where examination of structure is easy.

But this is not all. Function is more complicated than structure. Structure, so to speak, obtrudes itself on our notice; while function may hide itself away, and only be discovered after long searching. The liver, gall-bladder, hepatic ducts, and bile were evident to the ancients; and it was natural that bile formation should early have been recognised as a function of the liver. But a lapse of more than two thousand years separates this discovery from that of Claude Bernard, which taught us that the liver has other functions. Now, we believe that the liver forms sugar, plays a great part in proteid katabolism, destroys or excretes many bacterial and other poisons; we are a little nearer than the ancients to a full knowledge of hepatic function, but still a great way off.

**Health and Disease.**—The definition with which the chapter was opened may be taken as an index of the kind of difficulty with which we shall constantly meet in the following pages. The definition itself is straightforward and accurate; but what is disease? It is easy to reply that disease is the converse of health; but what is health? Health itself is a sum of variables,—indeed, in normal physiology we speak of "variations consistent with health." And if health is a sum of variables, what must be the case with disease, embracing as it does every conceivable condition which is not healthy, whether it be on the side of insufficiency or of excess? In many points the variables of health and of disease overlap. If we meet with a man in whose urine we find sugar, we at once declare him to be the subject of disease, and in the vast majority of cases we shall be right. But under certain circumstances a man in perfect health may excrete as much sugar in his urine as a diabetic patient, and perhaps every healthy person excretes a trace at all times. It is not, therefore, strictly correct to say merely from discovery of sugar in the urine that the man is a subject of disease. Nor can we take the presence or absence of symptoms as our guide, and look upon health as a mental state from which morbid symptoms are absent; disease as a state associated with the existence of morbid symptoms. For the man with an aortic aneurysm or bilateral paralysis of the abductor muscles of the larynx is still the subject of disease, though no symptom may give him warning of the fact. But it is in the case of chronic diseases that the absence of any border line between health and disease is most clearly recognisable. In many of them no period can be assigned to their onset, and health passes imperceptibly into disease just as infancy passes imperceptibly into old age.

It is therefore useless to attempt a definition of "disease";

one cannot define that which has no limits. Nor does it aid us to follow Cohnheim, and "speak of a disease *where the regulative mechanisms, acting in opposition to one or more vital conditions, are no longer adequate to secure that the various vital processes shall proceed undisturbed.*" For, as Cohnheim allows, this is but a paraphrase; it simply amounts to an assertion that in disease there is disturbance of that state of equilibrium which we call "health." Fortunately, however, a definition is the less needed, since abnormality of structure, or of function, or of both, in the majority of cases enables us with readiness to recognise the existence of *special diseases*, though we are unable to define the conception "disease" itself.

**"Organic" and "Functional" Disease.**—Diseases are often classified as organic and functional. This is a useful—at present even a necessary—clinical division, but it is at the same time a cloak for ignorance. It is inconceivable that an absolutely normal cell should perform its function abnormally. Hence it must never be forgotten that a functional disease is only one in which we are at present unable to correlate the abnormality of function which we recognise, with a definite abnormality of structure; the abnormality of structure is there, though we cannot point to it. When we speak of organic disease we mean that obvious structural changes exist upon which functional changes depend.

**The Scope of General Pathology.**—It is the duty of general pathology to correlate symptoms with structural changes and trace the connection between them. A patient, we will say, is suffering from shortness of breath, cough with bloody expectoration, pain in the side on drawing a deep breath, dropsy of legs and abdomen. Morbid anatomy teaches us that in cases such as these the right side of the heart is dilated, the left ventricle is perhaps dilated and hypertrophied, the flaps of the mitral valve perhaps thickened and irregular; it teaches us, further, that there are changes in the lungs,—that a part will probably be found solid and engorged with blood,—that the pleura over this part will be inflamed. Do the heart and lung conditions and the symptoms stand to one another as cause and effect? If so, which condition is primary,—that of the heart or that of the lung? How have the functions of heart and lung been modified by the changes in their structure? How have the functions of parts other than the heart and lung been affected by the alterations in these viscera? This is the kind of question that general pathology attempts to answer. It appeals to direct experiment, to morbid and normal anatomy, to physiology, to pharmacology, to chemistry, to physics; and with the aid of these, and, if necessary, other sciences, it strives, however feebly and imperfectly, to trace back symptoms to their causes and to unravel the processes of disease.

Nor is general pathology of a theoretical interest only. It is the one sure basis for diagnosis, for treatment, for prognosis. It is the one sure basis for diagnosis. A patient has on the toe a small indolent ulcer which has penetrated into the joint. He knows no reason why the ulcer should have appeared; he does not remember an injury to the toe; and only on close questioning do we find, perhaps, that a few days before the ulcer formed he pared a corn and drew a little blood. Without the aid of general pathology we should not know what to think, but, probably, since the ulcer looks trivial, we should regard it as such. And yet this would be a grave mistake, from which a knowledge of general pathology saves us. For general pathology teaches us that ulceration occurs when the resistance of tissues is insufficient to overcome the effects of an irritant. A slight abrasion, such as that which just removes the epidermis and draws blood, acting upon a normal tissue would lead to no ill results. In the case before us the same injury or irritant leads to ulceration. The conclusion is inevitable that our patient's tissues offer a diminished and not a normal resistance.

We carry the matter further back and ask ourselves the causes of lowered tissue resistance. We find that they are summed up in the word "mal-nutrition," and that mal-nutrition implies either insufficiency of blood-supply, or perverted nervous control of the tissues, or both. On further search we find that, though in our patient there is no evidence that circulation is specially impaired, there is ample evidence that nervous control of the lower limbs is abnormal. The patient walks with a peculiar gait, and sensation in the feet is impaired. Now we are on the right path, and by a similar process of reasoning we shall ultimately conclude that the ulcer is a manifestation of disease affecting the afferent tracts of the spinal cord. We no longer look upon the ulcer as trivial, but as having a terrible significance. General pathology has guided us to the correct diagnosis.

It is the one sure basis for treatment. One of the most important points to be remembered in studying disease—as in studying health—is the inter-dependence of tissues, and yet it is a point that is too often ignored. When a simple ulcer forms on the leg we often say that the *leg* is diseased; but when the ulcer is syphilitic, we say that the *patient* is diseased. But the body generally is involved in the case of a simple ulcer no less than in the case of a syphilitic ulcer. To mention only one point: the afflux of blood to the region of the simple ulcer cannot take place without inducing a corresponding diminution in the blood-supply of other parts. In both cases, therefore, the body generally is affected as well as the leg. But there is a difference between them; for, whereas, in the case of the simple ulcer the local condition is primary and the general condition secondary, in the case of the syphilitic ulcer the general condition is primary and the local condition is secondary.

Now the constant aim of therapeutics must be to combat causes of disease; in that path and in that path alone lies real success. So far as may be, treatment of mere symptoms must be avoided. And just as general pathology teaches us to concentrate our attention locally to the cure of the simple ulcer, so it teaches us that adoption of the same course is worse than useless in the case of the syphilitic ulcer. For the simple ulcer is the prime disease, the syphilitic ulcer is merely symptomatic.

It is the surest basis for prognosis. A clinician, with vast experience of his own and the accumulated experience of ages, discerning by physical examination of the patient that his aortic orifice is contracted, could prophesy the natural course of the disease without the aid of general pathology. But at best his prognosis would only be a probable one, and could only be derived from knowledge of similar cases. With the aid of general pathology, however, he might deduce the course of the disease from his knowledge of the relations between cause and effect in other parts. Experience could only teach him facts: general pathology teaches him the principles and laws underlying those facts. It teaches him that when muscle is called upon to overcome a greater but not an insuperable resistance, it contracts with more force; that, if the increased resistance continue to act, the muscle hypertrophies; that hypertrophy cannot go on indefinitely, but only up to a certain point; and that if the resistance is insuperable, after a few abortive contractions the muscle refuses to contract. With these data he can argue with safety in the case before him that the left ventricle will hypertrophy, and that as long as hypertrophy can keep pace with the increased resistance no symptoms will arise, but that a time will come when hypertrophy lags behind and the effects of increased resistance begin to show themselves, until at last the resistance becomes insuperable and the heart refuses to contract. He can apply the data to the urinary bladder, to the uterus, or to the biceps as well as to the heart; and the greater his knowledge of general pathology, the more confidence will he be able to repose in his prognosis in any individual case. Knowledge of a principle in general pathology will often guide him aright when his own personal experience fails.

Since, then, general pathology inquires into the principles and laws of disease,—since it must serve as the basis for diagnosis, for treatment, and for prognosis,—he is the sound clinician who builds his medicine or his surgery upon a knowledge of general pathology.

But there are many subjects in connection with disease which are of great interest and importance, which we are obliged to recognise, but concerning which general pathology can offer no explanation, or at best can only offer theories. Such, for example, are the effects of season, geographical and racial distribution of special diseases, inheritance in disease.

**The Effects of Season upon Disease.**—Medical statistics teach us that typhoid fever and rheumatic fever occur more commonly during the months of August, September, October, November than during any other months of the year. Scarlet fever is most common in September, October, and November. Measles occurs most in June and December, whooping-cough in spring and autumn, dysentery in summer and autumn, epidemic diarrhœa in summer and early autumn. The facts are clear, but their explanation is obscure. The diseases which show this seasonal prevalence are, speaking broadly, characterised by their "infective" nature, and this we have learned to associate with the presence of micro-organisms. But of the diseases mentioned above we can only point to one—typhoid fever—in which evidence as to a microbial cause even approaches to *scientific* certainty, though it is *morally* certain that most, if not all, of the others are also caused by micro-organisms. Nor do we know how the particular climatic conditions act, though we cannot but expect that the two conditions most intimately concerned are temperature and moisture. We generally assume that certain degrees of moisture and of warmth at those seasons favour a multiplication of the micro-organisms, and thus lead to the greater incidence of the specific diseases. We ignore the personal element. But there is evidence that the body itself varies at different seasons. Ringer observed that the antagonism of pilocarpin and muscarin in their action on the frog's heart varies in different months. In summer months the antagonism is always strong; in winter months it is very slight, or there is no antagonism at all. The antagonism of atropin and aconitin shows similar differences. The peculiarity is due to temperature; for, if in winter frogs are kept for several days at 15·5 C. (60° F.), antagonism becomes well marked and as strong as in summer months. Gürber, too, found that the livers of rabbits contain in the summer months only about one-third of the amount of glycogen that they contain in the winter months, and this although the food in summer and in winter was the same.[1] It is obvious, therefore, that general pathology cannot at present render us much help in explaining the seasonal prevalence of certain diseases.

---

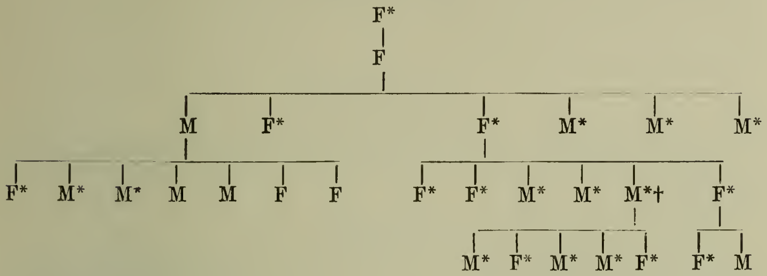
[1] In acute pulmonary tuberculosis, as I have shown (*Lancet*, 1891, vol. ii.), there is a seasonal variation, the patient's fever and the activity of the disease being greater in hot weather than in cold. Comparison was made in this respect between July and January.

**Geographical and Racial Distribution of Special Diseases.**—We have also to acknowledge that certain diseases show special geographical and racial distributions. Chorea is said to be unknown in China; granular kidney and renal diseases generally affect dwellers in the temperate zones; malaria and malarial fevers are principally found in the tropics. Even in England alone we see the same differences. Calculus of kidney and bladder is more common in Norfolk than in other counties; heart disease is especially common in districts which, from their physical configuration, are protected from winds (Havilland).

The influence of race shows itself in the following instances. The "sleeping sickness" is a disease of negroes, but they are said to be exempt from hæmorrhoids and varicose veins. Gout is "common in certain races and communities, but very rare, perhaps non-existent, in others. Roughly speaking, it is a disease of the ruling races and the higher classes; of the civilised man, not of the savage; of the white man, not of the negro; of cold and temperate rather than of hot climates" (Beddoe). Yellow fever, in the countries where it is endemic, spares the negro and attacks the foreigner, especially the northern European. But here we have to do with susceptibility and immunity, a subject so important that it will need special discussion.

**Inheritance in Disease.**—One of the most certain, but at the same time one of the most inexplicable of facts connected with disease is inheritance. There is no doubt that insanity, hæmophilia, gout, rheumatism, diabetes, the occurrence of certain structural malformations, show a marked tendency to run in families. Sometimes male and female descendants are affected indiscriminately. This is well shown in a case reported by Ebstein, in which there was an inherited tendency to malformation of the toes and fingers. Below is given the genealogical tree of the family, the affected members being marked with an asterisk, and " M " and " F " standing for " male " and " female " respectively.

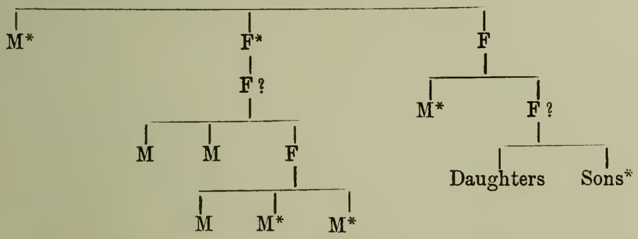
Genealogical tree of a family showing inheritance of malformation of fingers and toes.



† Wife had been previously married, and bore normal children to her first husband.

Sometimes the transmission is of a peculiar kind. Thus, hæmophilia is a disease which eminently, though not exclusively, affects males, but it is not transmitted by the males of a family who suffer, but by the females who do not suffer or suffer only slightly.

Genealogical tree of a hæmophilic family.[1]



We must, therefore, not expect too much from general pathology; it is still groping in the dark in many directions. Experience tells us a multitude of facts for which pathology can as yet offer no explanation or one which is only in part satisfactory. This will always be so, for there are no more difficult classes of question to answer than those which ask "Why?" and "How?"

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[1] This is the best " genealogical tree " in a hæmophilic family I have been able to find. It is recorded by Schrey and cited by Grandidier (Schmidt's *Jahrbücher*, etc., vol. cxvii., 1863, p. 330). As Schrey himself was a member of the family, the record possesses especial claims to accuracy. It will be noted that no descendants of males are found in the record; the reason of this probably lies in the fact that male bleeders usually die before they have attained manhood. " M " and " F," as in the previous case, stand for " male " and " female," an asterisk marks a person definitely hæmophilic, a note of interrogation marks a person in which the bleeding tendency was present, but only to a slight degree.

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# CHAPTER II.

## VEGETABLE MICRO-ORGANISMS, WITH ESPECIAL REFERENCE TO THE BACTERIA.

*Synopsis.*

I. Classification and Characteristics.

II. Vital Properties of Bacteria.
  (i) Reproduction.
  (ii) Motility.
  (iii) Aërobiosis and Anaërobiosis.
  (iv) Saprophytism and Parasitism.
  (v) Products of the Life History of Bacteria.
  (vi) Effects on Bacteria and their Products of Physical and Chemical Agents.
  (vii) Variability of Bacteria.
  (viii) Symbiosis.
  (ix) Pathogenicity.
  (x) Specificity.

It was not until the year 1873, when Obermeier discovered in the blood of persons suffering from relapsing fever a minute motile spiral micro-organism, that it became necessary to refer to these organisms in works upon pathology or medicine. It is true that so long ago as 1701 Andry had suggested the causal relation between them and disease; that in 1835 Bassi demonstrated that a fungus is the cause of muscardine, a disease fatal to silkworms; that Davaine in 1863 claimed to have proved that a micro-organism, now known as *Bacillus anthracis*, is the cause of a disease particularly fatal to cattle in certain portions of Europe; and that a little later Pasteur proved that "pébrine," another silkworm disease, depends upon a micro-organism which he constantly found present in the bodies of silkworms sick with or dead of the disease. But, in spite of the commercial value of the results obtained by Bassi, Davaine, and Pasteur, the facts they had discovered were isolated, and, above all, so far as could be seen at that time, had no more than a potential value for human pathology. When, however, Obermeier made his discovery, and when in 1877 Koch brought forward conclusive evidence that

Davaine's micro-organism is really the cause of anthrax, then it became clear that micro-organisms are of more importance in nature than for the purpose of deciding mere theoretical questions such as that of "spontaneous generation,"—a question which, it may be noted in passing, they had, by the time of which we are speaking, conclusively answered in the negative.

I. **Classification.**[1]—The vegetable micro-organisms with which we are concerned are fungi. Fungi have been classified in various ways by different authors. The division which will be adopted here is that of Nägeli, and is as follows:—

- I. Hyphomycetes, or true moulds.
- II. Blastomycetes, or saccharomycetes (yeast fungi).
- III. Schizomycetes, or fission fungi
  - Micrococci
    - Staphylococcus.
    - Streptococcus.
    - Diplococcus.
    - Sarcina.
  - Bacilli.
  - Spirilla.

Of these groups, by far the most important to pathology at the present day is that of the Schizomycetes, and they will consequently receive the greater amount of attention in this chapter. Since, however, many of the characteristics of the Schizomycetes are common to the rest of the fungi, statements made may be taken as true for the whole of the fungi, unless anything be said directly to the contrary.

The **moulds** are characterised by the existence of a mycelium or branched network of hyphæ. In some cases these hyphæ are divided into numbers of cells, in others the organism is unicellular. The moulds form spores, which are borne on the end of aërial hyphæ. They do not call for detailed notice here, as but few of them are known to be connected with disease.

The **yeasts** or **torulæ**, the best known example of which is *torula* or *saccharomyces cerevisiæ*, are budding fungi. The cells of which the organism is composed are spherical; though the greater number of the cells are of one size, yet there is not the uniformity of size that one meets with in the case of the micrococci, while the torula cell is considerably larger than even the largest micrococcus.

---

[1] Animal micro-organisms which are known or are supposed to be connected with disease will not be considered in this chapter, but along with the several diseases with which they are bound up.

**Micrococci** are spherical organisms, the spheres measuring on an average ·7$\mu$ in diameter. They are divided into classes according to the manner in which they grow. The **staphylococci** are so called because they grow in heaps which have been likened to bunches of grapes. **Streptococci** are so called because they form chains or chaplets. **Diplococci** are very closely allied to streptococci, and, as their name implies, are met with in pairs; a transparent capsule surrounds each pair of cocci, which, however, is lost on artificial cultivation of the diplococcus outside the body. **Sarcinæ**, so called from their likeness to bales of wool tied in directions at right angles to one another, are micrococci, in which division takes place in three planes.

**Bacilli** are rods, and it is essential that one diameter should be greater than the other. The difference between the two diameters varies very greatly; in the case of *B. prodigiosus*, the two diameters are so closely alike that for many years the micro-organism was regarded as a micrococcus; in the case of *B. tuberculosis* the average length (2·5$\mu$) is twelve times the breadth (·2$\mu$). The actual size of bacilli varies very considerably, some of the largest varieties being visible with ½in. objective, while most of the pathogenetic bacilla can only with difficulty be seen with a ⅛in. objective, and require $\frac{1}{12}$in. immersion lens for proper investigation. Even with this magnification and a correspondingly high eye-piece the influenza bacillus is very minute (length ·5$\mu$); it is the smallest pathogenetic micro-organism known.

**Spirilla**, as their name implies, are spiral micro-organisms. The number of turns in the spiral is very variable. In the case of the vibriones the spiral nature is only evident by so slight a curve that one of the family *V. choleræ asiaticæ* was originally named by Koch the "comma bacillus"; but on cultivation reversion may be made to the true spirillar form. In those forms which are known as spirochæta, and which are commonly to be found in water, as many as thirty complete turns of the spiral may occur.

The manner in which bacilli are arranged depends largely but not entirely upon the rapidity of their growth. Some bacilli, *e.g.*, *B. anthracis*, *B. filamentosus*, have a natural tendency upon artificial cultivation to grow out into long threads frequently composed of scores of individual bacilli; others, *e.g.*, *B. typhosus*, have but slight tendency to form threads, and at utmost two or three are joined together end to end.

II. **Vital Properties of the Bacteria.**[1]—(i.) **Reproduction.** One of the most noticeable facts concerning the bacteria is the rapidity of their multiplication. Under suitable conditions it is so rapid that a fluid which contained so few micro-organisms as to be perfectly limpid, in the course of twenty-four hours becomes cloudy or even quite turbid from the numbers present. The methods of reproduction of the bacteria are essentially two, viz., direct division and spore-formation. In direct division (it is from the constancy with which this characteristic is present that the schizomycetes or fission fungi are so called) the bacterial cell, whether bacillus, micrococcus, or spirillum, simply divides transversely into two; these again sub-divide transversely, and consequently multiplication after this method goes on in geometrical progression. No case is known in which a bacterium divides at a given time into more than two segments. Division occurs in some cases by the formation of a slight constriction in the wall of the micro-organism which divides it approximately into two equal segments; at this point a septum is formed and division is complete; in other cases no constriction appears, but only a septum. The two daughter bacteria, after growing to the size of the parent cell, again sub-divide in the same manner.

If the conditions for growth are very favourable, the daughter cells may sub-divide before reaching the size of the parent cell. Under these circumstances the final product is, for a time, a smaller-sized variety than the original; but when, owing to the rapid growth and the consequent diminution in the amount of nutriment available, the conditions have become less favourable, the length of time between two consecutive divisions is increased, the period of growth previous to division is longer, and the healthy descendant is apparently similar in every respect to the healthy parent. This condition is particularly noticeable among the bacilli, and the amount of difference produced may be remarkable. In the case of the micrococci it is not known to occur, and, therefore, on microscopic examination all the micrococci in a culture are, as has already been said, of the same size. Rapidity of growth, however, is not without effect upon the characteristics of certain of the micrococci, viz., the streptococci. It is frequently noticed that the number of cocci which go to form a chain is less according as the rapidity of growth is greater; moreover, it is obvious that the appearance of a coccus in the act of division is similar to that of a diplococcus, and in a rapidly-growing culture of streptococci the number of diplococcus-forms is apt to be greater than in the case of a culture which has grown less rapidly, owing perhaps to exposure to a less favourable temperature.

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[1] The term "bacteria" is a loose but convenient one, under which are included all varieties of fungous vegetable micro-organisms, excepting perhaps the true moulds and the torulæ.

The rate at which division takes place in bacteria varies very considerably, and according to a variety of circumstances, such as composition of nutrient culture-medium, temperature, presence or absence of oxygen, etc. The consequence is that bacteria have apparently very varied rates of growth: thus *B. tuberculosis* requires several weeks to present as copious a growth as is presented by *B. subtilis* in twenty-four hours. At first sight one might imagine that this implies a difference in the rate of division of the two bacilli, quite apart from the circumstances under which the two micro-organisms are placed, but it is more probable that the difference lies in the fact that, whereas a highly suitable culture-medium has been discovered for *B. subtilis*, so suitable a medium has not yet been discovered for *B. tuberculosis*, and, therefore, that comparison in this respect is not justifiable.[1]

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[1] In the case of *B. subtilis* fission is complete in about twenty minutes. If

So far as the plane of division is concerned micrococci can apparently divide in any plane; amongst the bacilli, division in the long axis has not been proved to exist, though it has been described, but there is no doubt concerning the frequency of division in the short axis.

Reproduction by spore-formation is a special method whereby the persistence of the species is assured. It is not known to occur among either the staphylococci, streptococci, or the sarcinæ, occurs but rarely and in a special form among the blastomycetes, is fairly common but by no means invariable among the bacilli, and is the rule among the true moulds. From the point of view of pathology, spore-formation in the bacilli is of most importance, and bacilli have been divided into two classes, **sporogenous** and **asporogenous**, according as they do or do not form spores. As examples of sporogenous bacilli may be given *B. anthracis* and *B. tetani*, while *B. typhosus* and *B. diphtheriæ* are examples of asporogenous bacilli. Spores in the case of bacilli are formed "endogenously," that is to say, in the body and at the expense of the protoplasm of the bacilli. They are oval or occasionally spherical, highly refractile bodies, whose short diameter is frequently greater than the short diameter of the bacillus in which they lie, and which is therefore stretched by them. One spore only is contained in each bacillus, and the position which it holds differs in different species, but is remarkably constant for the same species. In most cases the spore is central (*B. megatherium*) or slightly nearer to one end of the bacillus (*B. anthracis*), but in some cases the spore is situated at the extreme end of the bacillus (*B. tetani*), and gives rise to a drumstick appearance.

In the blastomycetes the only form of spore-formation that is known is ascosporous. In this case one of the spherical cells forming the yeast enlarges, divides by septa at right angles to one another into four cells, which become rounded off, and finally come to lie loose in a sac (ascus) formed by the original outer covering of the mother cell. In the case of both endospores and

division were to proceed in geometrical progression at this rate for seven hours only, the progeny of each bacillus would number over a million.

ascospores the spores are set free by the dissolution or bursting of the membrane—bacillus or ascus—which contains them.

In cultures of streptococci, and to a less degree in cultures of staphylococci, it is frequently noticed that one or more of the cocci is larger and stains more deeply than its neighbours. It has been supposed that these large, darkly staining elements are of the nature of spores, but of this there is at present no proof.

Concerning the conditions of spore-formation but little more is known than that it is in most cases dependent upon the presence of a free supply of oxygen, and that by the adoption of certain means it may be kept in abeyance for a longer or shorter period. Thus in a broth cultivation of *B. anthracis* spore-formation is far more copious on the surface of the fluid than in the depth; in fact, Klein asserts that spore-formation does not occur in *B. anthracis* except in the presence of free oxygen, and therefore does not occur at all in the depth of a broth cultivation. Be this as it may, it is certain that by adding small quantities of carbolic acid (·04 per cent.) or potassium bichromate to the culture-medium, or by growing the bacillus at an elevated temperature (42·5° C.), it is possible to obtain a variety of *B. anthracis* which for an indefinite number of generations forms no spores so long as the artificial conditions are kept up, and, indeed, may have lost the power of forming spores when again transferred to normal culture-media and normal limits of temperature. No case of spore-formation is known to take place in the animal body, even in the case of bacilli which are known to form spores readily outside the body. Schreiber, whose work on the physiology of spore-formation is the latest and fullest that we possess, considers that conditions which produce a sudden check to a growth which is going on rapidly and under favourable conditions, are particularly favourable for the rapid and full formation of spores; such hindering conditions are best attained by adding sodium carbonate, magnesium sulphate, sodium chromate, or even distilled water to the culture during growth. He also finds that the presence of oxygen is necessary for spore-formation among aërobic bacteria. In the case of sporogenous anaërobic bacilli this condition, of course, cannot come into play.

(ii.) **Motility.**—Many of the lower forms of vegetable life are actively motile, but the motility varies in degree and in kind. In the group of organisms now under consideration motility is only known to occur among the bacilli and the spirilla: true moulds, staphylococci, streptococci, sarcinæ are motionless with the single exception of *Micrococcus agilis.* Though all spirilla, including therewith the vibriones, are, at some period or other of their existence, motile, the bacilli do not show a constant rule in this respect; thus *B. typhosus* is actively motile, *B. anthracis* is always motionless. Motility in the case of micro-organisms is carried out by means of flagella, which are fine filaments attached to the body of the bacterium or to its outer coat. The number of flagella on a micro-organism varies very largely, and is by no means constant for one and the same species, though certain broad statements may be made as to the number of flagella which a given species of bacterium possesses. The length of the flagella also varies, but in most cases the flagella are individually longer than the bacterium to which they are attached, and in many instances they are two or three times that length. Speaking generally, the flagella of spirilla and vibriones are shorter than the flagella of bacilli. The degree of motility of the micro-organism bears no evident ratio to the number of the flagella present; the vibriones, which are very actively motile, are provided with one, or at most two, flagella attached to one end of the vibrio,[1] but on the other hand the sluggishly moving *B. tetani* can be seen on appropriate staining to be surrounded on all sides by so many flagella as to form a somewhat dense network. In the case of the spirilla, too, the same lack of ratio is also visible; though, as a rule, all varieties of spirilla are provided with one or two flagella at either end, the difference in the rate of progression of different varieties of spirilla is very marked.

The motion which is impressed upon a bacillus by its flagella is different from that which spirilla and vibriones undergo. The bacillus moves, as a rule, straight forward, but can turn from side to side apparently at will; spirilla, on the other hand, rotate on their long axes and therefore have a cork-screw movement; they can apparently move in either direction forwards or backwards; vibriones move in a zigzag fashion, but this is probably in nature identical with the cork-screw movement of spirilla, for the optical appearance presented by a very short spiral or rather portion of a spiral (such as is a vibrio), when rotating on its axis, is that it is pursuing a serpentine or zigzag course.

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[1] Vibriones are occasionally seen bearing flagella at both ends.

Motility bears a very close relation to the age of the culture, being more active in proportion to the youth of the culture. The converse, viz., that the older the culture the less actively motile the bacteria, is also true; if a culture be kept for some days, a very large and increasing number of bacteria is found to be completely motionless, and on staining the number of bacteria showing flagella is small. Besides age of culture, temperature and the presence of oxygen have important effects upon motility. Lowering the temperature diminishes, and, within certain limits, raising the temperature increases, the rapidity of movement. The effect of oxygen is best seen in the case of aërobic bacteria. Most motile aërobic bacteria are characterised by the fact that in broth culture a thick scum of bacteria forms rapidly on the surface of the liquid, and that this characteristic, the motility and the obtaining of oxygen have somewhat in common, may readily be seen in the following way. If a drop of a broth culture of *V. choleræ asiaticæ* be placed on a coverslip and this be inverted over a well-slide, care being taken to prevent drying of the drop, it will be noticed, on microscopic examination with a high power, that the vibriones are in active movement and that the general direction of their movement is towards the margin of the hanging-drop. When they have reached the edge of the drop their movement slackens and some of them may come completely to rest. If such a drop be left undisturbed for a quarter of an hour or so, by far the larger number of the vibriones will be found to have collected at the edge of the drop, where they will form a dense motionless or quivering mass: it is in this situation that the fullest opportunity presents itself for obtaining oxygen. In the centre of the drop fewer vibriones will be found, the motility of which, assuming temperature and other factors to have remained constant, will be practically unimpaired.

(iii.) **Aërobiosis and Anaërobiosis.**—The question whether the growth of a micro-organism is better in the presence or in the absence of oxygen is one of considerable importance, and has led to the formation of the two great classes of aërobic and anaërobic bacteria. Of these, so far as is at present known, the aërobic class is the larger, but the anaërobic class contains many important members, such as *B. tetani*, *B. œdematis maligni*, and the bacillus of quarter-evil. The principal difference in this respect between aërobic and anaërobic bacteria is, that while many aërobic bacteria are capable of multiplying under relatively anaërobic conditions, no anaërobic micro-organism is capable of multiplying under aërobic conditions. It is true that an aërobe does not grow so readily under anaërobic conditions as under aërobic conditions, but nevertheless growth takes place; but if an anaërobe be kept under aërobic conditions, or even if more than the minutest trace of oxygen is present, the anaërobe completely refuses to grow. Bacteria may therefore be divided, so far as this matter is concerned, into strict or obligatory aërobes, facultative anaërobes, and strict or obligatory anaërobes.

Though growth may be completely absent if an aërobe be placed under anaërobic conditions, or an anaërobe be placed under aërobic conditions, the aërobe or anaërobe has not lost the power of multiplication; it is only necessary for air to be admitted to the aërobe and to be excluded from the anaërobe, and growth will take place (other conditions being assumed favourable) with great rapidity.

The pathological importance of aërobiosis and anaërobiosis is evident from the fact that the animal body presents opportunities for either aërobiosis, facultative anaërobiosis, or anaërobiosis. The first may be obtained on the surface of the body and in the lungs, possibly in the blood; the second is possible in all the tissues; the third is obtained with difficulty, but the multiplication of bacteria in the intestinal tract probably takes place under anaërobic conditions; elsewhere it is highly probable that anaërobic bacteria can only multiply if they be associated with aërobes, the growth of which consumes the limited quantity of oxygen present. It is obvious that no purely superficial condition can be due to the action of anaërobic bacteria.

(iv.) **Saprophytism and Parasitism.**—A saprophyte is an organism whose existence can only be carried on outside the animal body; it grows on and draws its nourishment from dead vegetable and animal matter, but is incapable of growth in living tissues. A parasite, on the other hand, can grow in and draw its nourishment from living tissues. As in the case of aërobiosis and anaërobiosis, so here no hard and fast line can be drawn between saprophytes and parasites, and the formation of an intermediate class is necessary. Thus we speak of strict or obligatory saprophytes, facultative saprophytes, or parasites, strict or obligatory parasites. As examples of the first class may be given most of the true moulds; as saprophytes which are at the same time facultative parasites, actinomyces and *Aspergillus niger* may be mentioned; all the pathogenetic micro-organisms which can be cultivated on artificial media and carried on from generation to generation outside the body are examples of parasites which are at the same time facultative saprophytes, while it is at all events conceivable that some of the micro-organisms, *e.g.*, *B. lepræ*, *Sp. Obermeieri*, the hæmatozoa (amongst which, perhaps, *Sp. Obermeieri* ought to be included), which have hitherto resisted all attempts at cultivation, are obligatory parasites.

The degree of adaptability of which bacteria are capable varies within very wide limits. Thus at the one extreme lie the aspergilli, which only on rare occasions multiply after they have gained access to the animal body; at the other extreme lie such organisms as those of influenza, gonorrhœa, and pneumonia, which can only maintain an existence outside the animal body under very special conditions, and even then very readily succumb. Between these extremes there is a large number of micro-organisms, such as actinomyces, *B. anthracis*, *B. typhosus*, which not only readily grow if they gain access to the body, but also may for an almost indefinite time carry on an existence on artificial media outside the body.[1]

The questions of saprophytism and parasitism are of great importance in pathology and medicine from a prophylactic point of view. It is obvious that if a micro-organism which is causing disease be only capable of carrying on a parasitic existence, segregation of the sick person is sufficient to stop the spread of the disease or to confine it to his immediate attendants. If, on the other hand, the micro-organism be a facultative saprophyte, segregation must be coupled with disinfection of any material which may leave the patient. For such material may contain the specific bacteria; and these, being capable of further growth outside the body, will be a source of danger to other individuals, possibly at a considerable distance in space from the original patient and at a considerable length of time after the disease in him has run its course.

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[1] In this connection there is a further point which will need discussion when we come to consider the questions of pathogenicity, infection, and susceptibility to disease, viz., that if the resistance of the animal be lowered, an otherwise obligatory saprophyte may, for the time, become a facultative parasite.

(v.) **Products of the Life History of Bacteria.**—The products of the life history of bacteria are of many kinds. We shall confine our attention to the following:—Pigments, acids and alkalies, gases, phosphorescence, enzymes. Along with the last named will be considered the products of ferment action and alkaloidal substances, the whole group including those bodies known as toxins, ptomaines, etc.

(*a*) *Pigments.*—Many micro-organisms, such as *B. prodigiosus*, *Sarcina lutea*, *B. pyocyaneus*, *Torula nigra*, form pigments, frequently in large quantities. The pigment is a distinct product of the bacterial cell, and does not form an integral portion of that cell but lies outside it. In some cases (*B. pyocyaneus*) the pigment diffuses into the medium upon which growth is taking place, in others (*B. prodigiosus*) the pigment does not diffuse but remains confined to the region of growth. Most of the pigment-forming or chromogenetic bacteria grow more readily at a temperature of about 20° C. than they do at body temperature (37° C.), but whether that be the case or no, there is no doubt that pigment itself is formed with difficulty or is not formed at all excepting at temperatures not far removed from 20° C. In this respect, raising the temperature is far more potent than lowering it. A chromogenetic bacterium may be rendered completely achromogenetic by repeated cultivation at 37° C., though as a rule such an artificially produced achromogenetic bacterium gradually regains its power of forming pigment if it be again repeatedly cultivated at 20° C. Speaking generally, chromogenetic micro-organisms are not pathogenetic; nevertheless, many of the pus-forming bacteria and certain others are exceptions to this statement.

(*b*) *Acids and Alkalies.*—These properties have been taken together for convenience, but the acid-forming and the alkali-forming bacteria are actually widely different.[1] Amongst the acid-producers the bacillus which causes butyric acid fermentation and *B. acidi lactici*, which is a frequent cause of the souring of milk, may be mentioned: the amount of acid that may be formed is very considerable. Acid formation in the case of *B. diphtheriæ* has been shown by Cobbett to be intimately bound up with the presence of carbohydrate in the culture-medium; it is probable that this fact is also true in the case of other micro-organisms. There is reason to believe that the hyperacidity of the gastric juice noted in some cases of dyspepsia depends upon acid bacterial fermentation.

Among the alkali-producers one of the most important groups is that which induces alkaline fermentation of urine principally by the conversion of urea into ammonium carbonate. In the case of *B. diphtheriæ*, Cobbett finds that, in the absence of glucose, an alkaline body is produced. As will be seen later, the amount of toxin formed by such micro-organisms as form toxins largely depends upon the reaction of the culture-medium during the growth of the micro-organism.

(*c*) *Gases.*—Among the many bacteria that form gases during their growth may be mentioned the putrefaction bacteria, *B. tetani* and *B. coli communis.* The gases formed are principally carbonic dioxide, sulphuretted hydrogen, marsh gas, hydrogen, but small quantities of many other gases may also be present. They are important pathologically in that during life putrefactive changes may take place in dead tissues with the evolution of gases which from their qualities or their quantities may lead to secondary morbid conditions. Thus the cardinal symptom of ozæna, viz., the intolerable stench which accompanies patients with this disease, depends upon the gases formed during the putrefaction of dead bone, mucous membrane, and mucus in the nose. The flatulent distension of dyspepsia, too, is of bacterial origin. In a very careful work Theobald Smith has shown that gas-formation depends upon the presence of carbohydrate in the nutrient medium, and that in the complete absence of carbohydrate such eminently gas-forming microbes as *B. coli communis* and *B. tetani* fail to produce even the slightest trace of gas.

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[1] Cobbett gives reasons for believing that *B. diphtheriæ* normally forms both acid and alkaline bodies, the relative amounts of which depend upon the constitution of the culture-medium—at all events, in part. On the whole subject of acid- and alkali-production by bacteria, *cf.* PETRUSCHKY, *Cent. f. Bakt.*, etc., vols. vi., 1889, vii., 1890, and xix., 1896.

(*d*) *Phosphorescence.*—Though of extreme beauty this property, so far as is at present known, is of no pathological significance. It is characteristic of certain putrefactive and other micro-organisms, and is most marked in the case of young and vigorous cultures.

(*e*) *Ferment-like Bodies and their Products: Alkaloidal Bases.*—In this group are contained the most important of the products of the vital activity of bacteria. Some of the members of the group are harmless, others are possessed of poisonous properties such as are equalled by no other bodies with which we are as yet acquainted. The most widespread of these bodies is one which is closely akin, so far as action is concerned, to pepsin and trypsin; it is effective in very small quantities, is readily destroyed by heat (an exposure to a temperature of 60° C. "killing" it in ten minutes); it is carried down along with any solid substance which is suspended in or precipitated from the fluid in which it lies; by its action on proteids it produces albumoses and peptones; in some cases it acts better in an acid medium, but in the majority of cases an alkaline medium is more favourable;[1] it causes solution of solid proteid substances, such as solidified blood-serum and gelatine, and besides albumoses and peptones the destruction of the proteid is accompanied by the appearance of such bodies as leucin, tyrosin, indol, etc. Its presence or absence has led to the separation of the two great classes of liquefying and non-liquefying bacteria. Most of the bacteria of putrefaction are liquefying (in fact liquefaction and putrefaction in this connection are almost synonymous terms), so also are *B. anthracis*, *B. tetani*, and many of the pus-forming microbes; on the other hand, *B. diphtheriæ*, *B. typhosus*, *Strept. erysipelatis* are non-liquefying. But besides the liquefying or peptonising enzymes other ferment-like bodies are also formed by bacteria. Thus a rennin-like enzyme which causes coagulation of milk is formed by many of the vibriones and by many of the bacilli which are grouped under the name of *B. coli communis*: bodies acting like amylolytic and inverting enzymes are also known to be produced by bacteria.

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[1] Possibly, therefore, we have to do with two distinct bacterial peptonising enzymes.

In this division of the subject must be included also all the poisonous chemical substances, be they enzymes, albumoses, or other protein bodies, or alkaloidal substances to which those bacteria which produce disease owe their powers. In the case of *B. diphtheriæ*, Roux and Yersin, and Martin have given reasons for believing that the toxic body is an enzyme, Hankin separated a toxic albumose from cultures of *B. anthracis*, Brieger separated a variety of toxic alkaloidal bases from the products of putrefactive bacteria. Wesbrook, bearing in mind the character of enzymes which leads them to cling to any substance which may be in their neighbourhood, has suggested that the true toxic substance of cholera is of the nature of an enzyme; and that the so-called tox-albumoses, toxo-globulins, toxic alkaloids found in cultures of the vibriones really owe their poisonous properties to the presence as a contamination, along with the albumose, globulin, or alkaloid, of a minute trace of the true ferment-like toxic body. Indeed, this view has been suggested as applying to all bacterial toxins. Be this as it may, and in our present state of ignorance concerning the chemical composition of ferments it is impossible to decide the question one way or the other, there is no doubt that certain bacteria, as the result of their life history, form bodies which, from their poisonous action on animal life, may be spoken of under the general name of "toxins." The toxins are usually prepared from broth cultivations of any given micro-organism, and indeed a culture from which the micro-organisms have been separated by filtration is frequently spoken of as "toxin"; thus, diphtheria toxin usually means a filtered culture in broth of diphtheria bacilli, though it is obvious that the filtrate contains many other substances besides the true toxic substance. The most potent toxins known are diphtheria toxin, which can, under suitable conditions, be obtained of such a strength that ·01 c.c. of the toxin (filtered culture) kills a guinea-pig weighing about 400 grams in forty-eight hours, and tetano-toxin, which, according to Kitasato, is so powerful that ·00001 c.c. of a filtered broth culture of *B. tetani* is sufficient to kill a mouse.

The formation of toxin in a culture depends upon a variety of circumstances. Not only is the nature of the species of importance, so that, *e.g.*, *Streptococcus erysipelatis* forms a much less powerful toxin than *B. diphtheriæ*, but also differences obtain between different varieties of the same species; thus some varieties of *B. anthracis* do not form a tithe of the toxin that is formed by others. The presence or absence of oxygen, the composition of the culture-medium, and particularly the presence or absence of carbohydrate therein, the degree of alkalinity of the culture-medium, the question whether growth took place undisturbed, or whether the culture was shaken during growth, the age of the culture, the presence of other than the specific micro-organism in the culture, or the purity of the culture, are all matters of great importance in determining whether much or little toxin shall be formed.

The toxins which have been described above are all to be found in the filtered cultures in which the specific bacteria have grown: they are extra-cellular. Within the last few years it has been found that, besides extra-cellular poisons which are the results of the metabolic activity of the micro-organisms and are specific, another variety of poison is to be found in the case of certain bacteria which is confined in the protoplasmic bodies of the bacteria, or, in other words, is intra-cellular. Intra-cellular poisons are formed by a variety of micro-organisms; their action, if injected into the peritoneal cavity of a guinea-pig, is approximately the same in the case of all bacteria which form these poisons, and consists, if a sufficient dose be given, in the production of an intense, extensive, and rapidly fatal (18–24 hours) peritonitis. But the interesting point is that many recognised non-pathogenetic micro-organisms, such as *B. subtilis*, *B. proteus vulgaris*, contain these poisons, while such undoubtedly pathogenetic microbes as *B. diphtheriæ* and *B. choleræ gallinarum* do not. The results obtained by the injection of the bodies of such microbes as form intra-cellular poisons do not differ whether the bacteria which contain them be injected in a living condition or have been killed by heat previous to injection, except that in the latter case a larger amount must be given to produce the same result. The significance of intra-cellular poisons is quite unknown, but it may be mentioned in passing that Klein believes that intra-cellular substances—not toxic—have an important part to play in the formation of antitoxin in the case of *B. diphtheriæ*.

In spite of their vast agricultural and hygienic importance it is not necessary to speak here of the properties possessed by certain bacteria of reducing nitrates with the formation of ammonia and free nitrogen, or, on the other hand, of oxidising ammonia with the production of nitric acid and nitrates.

(vi.) **The effects upon Bacteria and their Products of Physical and Chemical Agents.**—(*A*) *Physical Agents.*—(*a*) *Temperature.*—Every micro-organism has its optimum temperature for growth and minimal and maximal temperatures beyond which growth ceases. For the greater number of bacteria found in temperate climates the optimum temperature is 18°–20° C., viz., the temperature of the air; within these limits are the most favourable temperature conditions for reproduction, whether simple fission or spore-formation. Such bacteria as are commonly found in water, air, soil belong to this category. For other micro-organisms, including those which are pathogenetic for warm-blooded animals, the optimum temperature is 36°–38° C.

For the so-called thermal bacteria the optimum temperature varies in individual cases between 50° C. and 70° C. This class, members of which have been discovered by Miguel, Van Tieghem, Globig, Karlinski, Macfadyean, and Blaxall in water, soil, and thermal springs, is as yet a bacteriological curiosity, but it is probable that some of its members are of considerable importance. That certain putrefactive changes occur under conditions of very high temperature is readily seen in the case of the putrefaction of a manure heap; it is possible, too, that the so-called "spontaneous combustion" of haystacks may be due directly or indirectly to the action of thermal bacteria. For all practical purposes, however, they may be left out of consideration.

The actions of heat and cold upon bacteria are very different. It may be broadly stated that reduction of temperature below the optimum tends to inhibit growth but not to kill the bacteria, whereas elevation of temperature above the optimum not only tends to inhibit growth but also tends to kill the bacteria. Since, in addition, a far smaller rise of temperature produces the same result as a far greater fall of temperature, it is evident that, so far as bacteria are concerned, heat is a much more potent agent than cold. Frisch (1877) exposed various cultures of bacteria to a temperature of −87° C., which he obtained by the evaporation of liquid carbonic acid gas, and found that, even after exposure to such a temperature, micrococci and bacilli multiply abundantly when again placed under favourable conditions. Prudden also made extended experiments upon the influence of freezing; he found that, though differences obtain, nevertheless bacteria are able to withstand freezing for many days. One of the most marked of his examples is *B. typhosus*, which was found to be capable of growth after bearing continuous freezing for 103 days. Repeated freezing and thawing was found to be more fatal than continuous freezing.

In considering the effect of heat upon bacteria, one is, at the outset, met by the fact that a marked difference obtains between the effects of dry and of moist heat. This was clearly brought out by experiments instituted in 1881 by Koch and Wolffhügel, who found that, if dry heat be employed, the micro-organism being in a desiccated condition and spores being absent, a temperature of 120°–128° C. must be maintained for an hour and a half to ensure destruction of all the species tested; if, however, spores be present (*e.g.*, spores of *B. subtilis* or *B. anthracis*), a temperature of 140° C. maintained for three hours is necessary. The effect of moist heat upon bacteria in the absence of spores is, on the other hand, much greater, by far the larger number being destroyed by a temperature of 58°–60° C. maintained for ten minutes (Sternberg). The non-pathogenetic bacteria have, as a rule, a higher thermal death-point than those which are pathogenetic. With regard to the thermal death-point of spores when exposed to the action of moist heat, Sternberg found that the spores of *B. anthracis* are destroyed by exposure to a temperature of 100° C. for four minutes. The spores of non-pathogenetic bacilli require a higher temperature or a more prolonged exposure for their destruction. For the certain destruction of all known spores by moist heat, their exposure to a temperature of 120° C. maintained for ten minutes is amply sufficient. The difference which obtains between the actions of dry and moist heat depends upon the greater penetrating power of the latter.

But heat not only kills bacteria if it be sufficiently great, it also may produce profound modifications of vital activity if the temperature be not so greatly raised above the optimum as materially to interfere with growth. Reference has already been made to the facts that prolonged cultivation at an elevated temperature (42·5° C. in the case of *B. anthracis*, the optimum being about 30° C.) may convert the normally sporogenous into an asporogenous bacillus, and that pigment formation is abolished in the case of chromogenetic bacteria by the same means (38° C. in the case of *B. prodigiosus*, the optimum being about 20° C.). But from a pathological point of view the most important fact is, that by cultivation of a pathogenetic micro-organism at a somewhat elevated temperature, its power to form its specific toxin is impaired and that, though the rapidity of multiplication of the micro-organism may not be appreciably modified. Such a micro-organism is said to be **attenuated**, and by repeated cultivation at the same elevated temperature a permanently attenuated variety may be obtained. Whether the primary effect is due to some modification of the vital faculties of the micro-organism, or is owing to the destruction of a toxin normally formed, it is impossible to say; with reference to the last-mentioned supposition, it is known that the toxicity of a filtered culture of *B. diphtheriæ* is markedly diminished by exposure for a few hours to a temperature of even 40° C. By gradually raising the temperature at which growth is taking place, and making a series of sub-cultivations at each individual temperature, a micro-organism may become "acclimatised" and grow well at a temperature which would certainly have completely inhibited growth of the original culture.

(*b*) *Desiccation.*—In a moist state bacteria may be kept for a considerable length of time without losing their vitality, though this power varies within wide limits in different species. Thus, *Strept. erysipelatis* loses its vitality on an agar culture after about a week, but *V. choleræ asiaticæ* may still be found living after nine months and *B. typhosus* and *B. prodigiosus* after so long as a year and a half (Sternberg). But desiccation is very fatal to bacteria, especially to those species which are pathogenetic. In many cases life is only maintained for a few hours; Pfuhl, however, found desiccated typhoid bacilli living after 8–10 weeks, and Löffler found *B. diphtheriæ* still alive after they had been kept 4–5 months in a dry condition. These statements, though true in the case of bacteria, are not true in the case of spores, which resist drying to an extraordinary extent and may be kept in a desiccated condition for an indefinite period without losing their power of germinating when they are moistened and exposed to other favourable conditions. Desiccation alone is apparently without effect upon the toxic products of bacteria. The solid residue of a filtered broth culture of *B. diphtheriæ*, which has been evaporated to dryness at a temperature below 40° C., is intensely and specifically toxic. Such "dried toxin" may be kept for an indefinite time without change in toxicity.

(*c*) *Light.*—Downes and Blunt in 1877 first called attention to the fact that light acts injuriously on bacteria, and that cultures may be sterilised by exposure to direct sunlight. Since then, Duclaux, Arloing, Gaillard, Moment, Roux, and others have studied the subject. As the outcome of this work it has been found that the growth of bacteria is impeded by light, that if the micro-organisms be exposed to direct sunlight they are destroyed, and that spores are destroyed more readily by light than are bacilli. Direct sunlight acts more unfavourably than diffuse light, and Arloing found that rays at the violet end of the spectrum are more potent in this respect than rays at the red end. Marshall Ward investigated the bactericidal action of light more closely. He concludes that the waves which form the infra-red, red, orange, and yellow portions of the spectrum have no action, but that bactericidal power "begins at the blue end of the green, rises to a maximum as we pass the violet end of the blue, and diminishes as we proceed in the violet to the ultra-violet regions." The fact that the bactericidal power of light resides in this portion of the spectrum, of course, suggests that chemical action plays some part in the process. Roux showed that access of oxygen is a necessary factor in the sterilisation of cultures by light, and Wesbrook, working especially with *V. choleræ asiaticæ*, found that the action of sunlight is twofold: it is destructive to the bacteria on which it falls if they be in free contact with air, but it aids the growth of those bacteria on which it falls (through its heating power) if the bacteria be *not* in free contact with air. By a series of careful experiments, he showed that in an ordinary test-tube broth cultivation exposed to sunlight, destruction of bacteria goes on at the surface, multiplication in the depth; this is true if the column of culture be of greater depth than 2–4 cm.; if the column be less than 2–4 cm. destruction of the bacteria alone takes place. He further found that free growth takes place in anaërobic cultures in an atmosphere of hydrogen though exposed to the strongest sunlight.

D'Arcy and Hardy, following up Würster's discovery that when evaporation takes place in direct sunlight "active oxygen" is formed, investigated the question whether "active oxygen" is formed in the bactericidal action of light. Using specially sensitised paper, and throwing on a moistened strip of it the spectrum of an arc-light, they found that Marshall Ward's area corresponds to the site of formation of "active oxygen." That the action is dependent upon light- and not upon heat-rays is shown by the fact that no "active oxygen" is formed if a strip of black paper be placed over the moistened sensitised paper in the region of the spectrum concerned. It may, therefore, be regarded as proved that the bactericidal action of light is essentially of an oxidative character.

With regard to the action of light upon toxins and toxin-formation there is some divergence of opinion. Wesbrook found that the virulence of those bacteria which he had grown in strong sunlight was not appreciably modified. In view, however, of the fact that sterile toxins are, according to most authorities, gradually destroyed by light, and of the numerous factors entering into Wesbrook's experiments, it is safer, if it be desired to minimise alteration in the toxicity of a filtrate, to keep it in the dark. In this connection it is perhaps worth mentioning that such experiments as have been made upon bacteria with Röntgen's rays show that these rays do not inhibit growth.

(*d*) *Electricity.*—The action of constant and of induced currents upon the growth of bacteria has been investigated by several authors; no effect seems to be produced unless the current be of great strength and its action be long continued. It is probable that even under those circumstances a large proportion if not the whole of the observed results are dependent upon the chemical substances produced by electrolysis in the solutions in which the micro-organisms are suspended. With regard to the action of electricity upon toxins, there is the widest divergence of opinion. D'Arsonval and Charrin found that interrupted currents of great frequency attenuate toxins; Marmier, working with snake-poison, diphtheria toxin, and tetano-toxin, on the other hand, says that he found not the slightest attenuation with currents of high frequency, but that constant currents and interrupted currents of low frequency destroy bacterial toxins by the formation of hypochlorites and free chlorine in the fluid in which these toxins are placed. Some authors have even gone so far as to assert that toxins may be converted into antitoxins by the agency of the constant current.

(*B*) *Chemical Agents.*—In this group are included all those substances which are known as antiseptics and disinfectants; they are of the most varied composition, but they will not be referred to here in detail; information upon this subject must be sought in special treatises on bacteriology and hygiene. It may be briefly stated, however, that antiseptics differ from disinfectants, in that whereas an antiseptic prevents further growth of bacteria, it does not of necessity kill those bacteria which are actually present and living at the time when the antiseptic is caused to act; a disinfectant, on the other hand, not only prevents growth, but also destroys such bacteria as may be present, and therefore sterilises the substance upon which it acts. Many of the so-called disinfectants are antiseptics only, and some are neither disinfectants nor antiseptics but mere deodorants. The chemical substances which act on bacteria can only do so if they are in a liquid or a gaseous condition. Solids, such as iodoform, thymol, etc., act as antiseptics by virtue of their solubility or volatility. A disinfectant, if used in weak solution, acts as an antiseptic.

(*a*) *Gases.*—Reference has already been made to the action of oxygen both when treating of aërobiosis and anaërobiosis and when dealing with the bactericidal action of light. Other gases, such as hydrogen, nitrogen, carbonic acid, to mention those which are most commonly met with in animal life, are inert so far as concerns their chemical action. Sulphuretted hydrogen, according to Frankland, is quickly fatal to *B. pyocyaneus*, *V. choleræ asiaticæ*, etc., but on the other hand Grauer found that it is without injurious action upon *B. tuberculosis*, *B. anthracis*, *B. typhosus*, and *V. choleræ asiaticæ*, even though these micro-organisms were exposed to the action of a stream of the gas for an hour. Chlorine, bromine, iodine, sulphur dioxide, and some of the haloid compounds have marked antiseptic or disinfectant effects.

(*b*) *Acids and Alkalies.*—Though, if both are used in very strong solution, the action of an acid is the same as that of an alkali, viz., bacteria and even spores are destroyed, yet a wide difference exists between the actions of weak solutions of these substances. Thus whereas the addition of ·1 to ·5 per cent. sulphuric acid to a neutral culture not only prevents further growth in it, but also in time destroys such bacteria as may be already present, the addition of the same amount of caustic potash will in most cases not only not impede but will actually favour the growth of the bacteria present. Indeed, it has been found in practical bacteriology, that copious growth only occurs when the culture-media (excepting potato, which is acid) have been rendered faintly but definitely alkaline before use.

(*c*) *Other Chemical Substances.*—Speaking generally, other soluble substances, be they salts, essential oils, coal-tar products, or whatever be their nature, are either inert or exert a feebly restraining influence on bacterial growth, unless they are used in strong solution. An important exception exists in the case of compounds of mercury, which are powerfully disinfectant, even in minute traces; thus mercuric oxycyanide was found by Boer to destroy anthrax bacilli in so small a degree of concentration as 1 in 40,000, and Sternberg found that perchloride of mercury destroys the spores of *B. anthracis* and *B. subtilis* in two hours when used in the strength of only 1 in 10,000.[1] Concerning the bactericidal action of blood-serum we shall have to speak later. On the other hand, substances are known which, in dilute solution, favour the growth of bacteria; such are the soluble carbohydrates (particularly dextrose), albumoses, and peptones. That various inorganic and organic salts, etc., favour and can even maintain growth in the absence of proteid matter other than that minute quantity which is contained in the bodies of the bacteria used for inoculation is shown by the fact that bacteria can in many cases multiply readily in such non-albuminous culture-fluids as those devised by Pasteur[1] and Uschinsky.[2]

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[1] It is necessary to remember in this connection that the condition in which micro-organisms and spores are presented to the disinfectant is of great importance; if the micro-organisms are collected into comparatively large masses or flocculi, or if they be suspended in a medium which is itself acted on by the disinfectant, then a longer exposure to, or a greater concentration of, the disinfectant becomes necessary. Thus, perchloride of mercury, which is one of the most valuable disinfectants at our disposal, coagulates albumen, and if, as is very likely to be the case in any attempt to disinfect animal substances or excreta, these latter contain albumen, the perchloride of mercury will form a coating of coagulated albumen around the micro-organisms, and thus will actually protect them in some degree from the action of the disinfectant.

(vii.) **Variability of Bacteria.**—This question may be studied from either a morphological or a physiological standpoint. With regard to the latter, so much has already been said upon the variations that may be induced in the products of vital activity of bacteria by different agents, that it is only necessary here to point out that from this aspect there is an almost infinite number of races of any one variety of micro-organism. Thus we have seen that *B. anthracis* may lose its power of forming spores, *B. prodigiosus* may lose that of forming pigment, while *Str. pyogenes* may have its power of forming its specific toxin reduced to a remarkable extent. Between the typical and the atypical variety in each case there is an endless number of individuals having intermediate characteristics.

But it is not only possible by artificial means to diminish or even abolish some particular function of a bacterium, it is also possible in certain cases starting from below to augment the exercise of that function. Thus, starting with a cultivation of *B. anthracis* which has artificially been "attenuated" to such a degree (*i.e.*, forms so little toxin) that it fails in reasonable doses to kill the highly susceptible mouse, we may, by successive inoculation of this attenuated bacillus through animals rising in their degree of resistance to anthrax, so increase the power of toxin-formation, that at last the attenuated bacillus has been converted into one possessing even a greater degree of virulence than is normally the case. It therefore becomes conceivable that a

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[1] Pasteur's fluid :—

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| Distilled water, . . . . | 100 parts. |
| Cane-sugar, . . . . . . | 10 parts. |
| Ammonium tartrate, . . . | 1 part. |
| Ashes of 1 gram of yeast. | |

[2] Uschinsky's fluid :—

| | |
|---|---|
| Water, . . . . . . | 1000 c.c. |
| Glycerine, . . . . . . | 3–4 c.c. |
| Sodium chloride, . . . . . | 5–7 grams. |
| Calcium chloride, . . . . . | ·1 gram. |
| Magnesium sulphate, . . . | ·2–·4 gram. |
| Bi-potassium phosphate, . . | 2–2·5 grams. |
| Ammonium lactate, . . . | 6–7 c.c. |
| Sodium aspartate, . . . . | 3·4 grams. |

definitely non-pathogenetic micro-organism may in course of time and under suitable conditions be so modified in one of its functions that it becomes definitely pathogenetic. Of this, however, we have as yet no proof, in spite of the fact, amongst others, that Buchner asserted that he had, after a long period of artificial cultivation, succeeded in converting the non-pathogenetic *B. subtilis* into the pathogenetic *B. anthracis*, with which morphologically it has so many points in common. Neither this nor any other similar assertion has stood the test of time.

With regard to the morphological variability of bacteria there is more difficulty. Owing to the extreme ease with which a bacillus whose length differs but little from its breadth may be mistaken for a micrococcus or, if it stain more deeply at the poles, for a diplococcus, the ease with which a vibrio may be mistaken for a bacillus, a diplococcus for a sarcina and *vice versa*; and owing to the fact that some bacteria, *e.g.*, *B. diphtheriæ*, *B. tuberculosis*,[1] are known (Klein and others) occasionally to form what are apparently mycelial hyphæ, while in artificial cultivation the species cladothrix forms chains of bacilli, it has been supposed that the species bacillus, streptococcus, spirillum, etc., are not distinct, but that "pleomorphism" exists, the same micro-organism now showing itself as a bacillus, now as a coccus, now as a spirillum, and so on. But the fact that pleomorphism of bacteria was far more commonly accepted in the early days of bacteriology, when methods were less exact and the dangers of contamination of cultures were less fully recognised than they are now, suggests that most of the cases of so-called pleomorphism were apparent rather than real. With regard to *B. diphtheriæ* and *B. tuberculosis* the matter is different. In the first place there is no room for doubt as to the accuracy of the observation, and in the second place it is well shown by the case of actinomyces that a micro-organism which under ordinary circumstances forms a definite mycelium may under extraordinary circumstances grow as a bacillus. We may in course of time be compelled to regard the true moulds as the ancestral type of all bacteria or to look upon the bacillary as one mode of growth of certain true moulds, but at present, though it is fully recognised that the conditions of growth exert a powerful influence upon the size of bacilli, cocci, spirilla, sarcinæ, it is nevertheless generally denied that a bacillus under any circumstances becomes a coccus, or a coccus becomes a bacillus; in other words, it is denied that pleomorphism of bacteria exists.

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[1] From this fact Coppen Jones argues that *B. tuberculosis* is really a mould, and proposes to call it "tuberculomyces" on the analogy of actinomyces.

(viii.) **Symbiosis.**—In all our previous remarks we have tacitly implied that the micro-organism was in pure culture, but as a matter of fact this is rarely, perhaps never, the case except under purely artificial conditions such as are obtained in the laboratory. In nature many varieties are living side by side, and it becomes necessary to enquire how the growth, etc., of one micro-organism proceeds, if in its life history it alone have not full play but be associated with other bacteria. Much attention has been directed to this question during the past few years, and there is no doubt that it will attract even more attention in the future. The two chief points for consideration are, (*a*) how does symbiosis affect the growth of a micro-organism? and (*b*) does symbiosis produce any modification in the products of the vital activity of that micro-organism? With regard to the first question, it must be remembered that microbes, even if placed under what are apparently exactly similar conditions, have markedly different rates of growth. To take an extreme example: *B. tuberculosis* grows but slowly at 37° C., *B. prodigiosus* at the same temperature grows rapidly; if, then, a liquid culture-medium be inoculated at the same time with both of these bacilli and be incubated for twenty-four hours, it will be found at the end of that time that *B. prodigiosus* is the only micro-organism recognisable. But since *B. prodigiosus* in its growth has used up certain constituents of the medium, and as the result of its vital activity has added certain other constituents to the medium, one cannot, *a priori*, say whether under the circumstances *B. tuberculosis*, which undoubtedly was present in a living condition at first, and would have multiplied in due course had it been unaccompanied, will multiply later or no. It is certain, therefore, that though several varieties of micro-organism may be at the initial moment present in the culture-medium, the conditions may be so much more favourable for the growth of one particular variety, that it and its progeny may crowd out its companions. This is the principle which is adopted for the separation of *V. choleræ asiaticæ* from the stools of cholera patients in which numberless other micro-organisms may be present. By selecting a culture-medium which is favourable for the growth of *V. choleræ* but relatively less favourable for the growth of other bacteria, *V. choleræ* multiplies quite out of proportion to the other microbes present, and the ease with which it is obtained in pure culture is thereby proportionately increased.

But growth of a micro-organism in a culture-fluid gradually comes to an end, partly as the result of exhaustion of the culture-medium (*cf. Str. erysipelatis*, which ceases to grow when it has used up the peptone in the culture-medium, as shown by Cobbett and Melsome), partly as the result of the accumulation in the culture-medium of the products of its own life history (*cf. Saccharomyces cerevisiæ*, the growth of which is stopped by the accumulation in the culture-medium of the alcohol which it forms, as shown by Pasteur). If, then, the original culture-fluid have been inoculated with several varieties of micro-organism, after the growth of one of them has come to an end, a second which has survived may find the culture-medium, as modified by the previous growth of the first, so suitable for its own requirements, that it may now commence to multiply with rapidity and in its turn yield so overwhelming a number of that particular variety as almost to constitute a pure culture. An example of this condition probably exists when *B. tetani*, an anaërobic bacillus, is introduced into the animal body subcutaneously through a slight wound or scratch and produces disease. The conditions under which it finds itself are not anaërobic, though the amount of oxygen present must be but limited. *B. tetani*, however, gains access to the animal body under natural conditions in such a way that it is almost absolutely certain to be accompanied by other and aërobic bacteria. These multiplying in the exudation from the wound or scratch and requiring oxygen for their growth, use up the limited amount of oxygen present and therefore provide anaërobic conditions in which now for the first time the *B. tetani* or its spores are able to grow. The after-production of the chain of symptoms which constitutes the disease then becomes perfectly simple.

A good example of the effects of symbiosis was discovered in 1894 by Metchnikoff. He found that when *V. choleræ asiaticæ* has apparently died (*i.e.*, fails to yield a culture when inoculated into fresh media in the ordinary way) it may be revivified by allowing it to grow on gelatine in the company of certain aërial micro-organisms; these latter, by producing some unknown changes in the gelatine, render it so eminently favourable for the growth of *V. choleræ* that even though this microbe is unable to multiply under the usual conditions—and it is normally one of the easiest of known micro-organisms to cultivate—it is now able to multiply without difficulty. The pathological and hygienic importance of such a fact can hardly be over-estimated. For some authorities hold it probable that the production of such diseases as cholera and typhoid fever is closely bound up with symbiosis, if not absolutely dependent upon it.

With regard to the second question, namely, does symbiosis produce any modification of the products of vital activity of a micro-organism? we have much less evidence at our disposal. Roux and Yersin consider that the progress of diphtheria—which depends, *cæteris paribus*, upon the amount of diphtheria-toxin produced by the bacilli and absorbed by the body—is much more unfavourable if the diphtheria bacilli in the fauces are accompanied by streptococci than if they are found in pure culture. Not only, however, has their view been opposed, but also, even if accepted, it would be difficult to assert that the reason depended upon an increased virulence of the products of the diphtheria bacilli rather than upon an actual increase in their number determined by symbiosis, or than upon a diminution in the vital resistance of the subject as the result of absorption of the products of the vital activity of the streptococci. However, that such a modification of bacterial metabolic products as we are now considering may quite possibly be induced by symbiosis, perhaps no one would venture to deny.

Symbiosis may be either obligatory or facultative, but too little is known upon the subject generally for us to enter into a discussion of these questions. It may be mentioned, however, that in the case of certain alcoholic fermentations (*e.g.*, that occurring in the manufacture of ginger-beer) the co-existence of two micro-organisms is absolutely necessary, the particular kind of fermentation not occurring in the presence of either of them alone.

(ix.) **Pathogenicity.**—In the course of the preceding pages the terms "pathogenetic" and "non-pathogenetic" have frequently been used. It is necessary now to consider what meaning should be attached to them. At the first glance it seems easy to say that they mean "causing disease" and "not causing disease" respectively, but when the question is looked into more closely, it is seen that the terms, as commonly used, tacitly imply more than bare etymology warrants. Let us take some concrete examples. We find that *Aspergillus niger*, which under ordinary circumstances is a harmless saprophyte, may occasionally gain access to the human body (particularly the lungs), and there lead to a severe broncho-pneumonia; that *B. diphtheriæ*, which causes severe disease in man, is without effect upon the mouse; that *B. anthracis*, which leads to disease in many warm-blooded animals, including man, may be injected in large quantities into the frog without effect. We find also that the effects of one and the same micro-organism are vastly different, according to the region of the body into which it is introduced; a virulent culture of *V. choleræ asiaticæ*, for example, introduced into the peritoneal cavity of a guinea-pig, produces severe peritonitis and death in twenty-four hours or thereabouts, but the same amount of the same culture injected into the subcutaneous tissue of another apparently similar guinea-pig produces but little constitutional effect, and merely a slight and temporary inflammatory swelling, or at most a localised death of the tissues and ulceration around the seat of inoculation. A cultivation of *B. diphtheriæ*, on the other hand, acts in exactly the opposite manner: injected into the peritoneal cavity of a guinea-pig, it produces slight and transient symptoms (so long as toxin be not introduced along with the bacilli); injected subcutaneously, it causes marked and increasing swelling, severe constitutional symptoms and death in perhaps 24–48 hours. It further appears that the previous treatment which the animal has undergone has a share in determining pathogenicity or non-pathogenicity. For we find that the hen, which normally is unaffected by *B. anthracis*, becomes affected with and ultimately dies of anthrax if previous to inoculation she have been immersed for a short time in cold water (Pasteur). So also an animal such as a rabbit or guinea-pig, which normally falls a ready victim to a subcutaneous inoculation with *B. diphtheriæ*, remains absolutely unaffected by many times the dose of bacilli which otherwise would have been fatal if, previous to inoculation, it has been subjected to an injection of diphtheria antitoxic serum. Nor is the age of the animal without importance, for we find that, whereas *B. anthracis* is non-pathogenetic for adult white rats, it is pathogenetic for young white rats. Next there is the fact that a microbe, otherwise non-pathogenetic for a certain species of animal, may become pathogenetic if it be associated with the products of another non-pathogenetic microbe: the bacillus of quarter-evil is non-pathogenetic for rabbits, yet if at the same time as the inoculation with bacillus of quarter-evil there be injected one or two cubic centimetres of a filtered culture of *B. prodigiosus*, which is also non-pathogenetic for animals, these animals become infected with the bacillus of quarter-evil and die (Roger). Lastly, to make the question even more difficult of solution, we find that in the case of almost any micro-organism, if the dose injected be large enough, the animal may be killed, as the result of the growth of that micro-organism. It is therefore seen that pathogenicity and non-pathogenicity are terms to which no absolute meanings can be attached, since they may depend at least upon (*a*) the species of the micro-organism, (*b*) the species of animal inoculated, (*c*) the seat of inoculation, (*d*) the previous treatment, if any, to which the animal has been subjected, (*e*) the age of the animal, (*f*) the presence or absence of other micro-organisms at the seat and at the time of injection, (*g*) the dose of the micro-organism used for inoculation. We cannot speak of *Aspergillus niger* as a pathogenetic microbe, because under exceptional circumstances it causes disease in man, any more than we can call *B. anthracis* a non-pathogenetic microbe, because it normally produces no disease in the frog.

Such micro-organisms as *B. lepræ* and *Sp. Obermeieri*, though constantly found associated with certain diseases, have not hitherto been artificially cultivated, and their pathogenetic power, however probable, is therefore not as yet scientifically proved. They *might* be, though it is in the last degree improbable, merely accidental concomitants of the diseases in question. The same lack of scientific proof obtains in the case of diseases such as malaria, tsetse-fly disease, etc., which are associated with the presence of hæmatozoa; and yet no one doubts at the present time that the particular hæmatozoa found in these diseases are pathogenetic and specific.

But being given that a micro-organism is pathogenetic, it is necessary further to consider upon what property or properties that pathogenicity depends. In such diseases as tetanus and diphtheria, where the specific microbe never, or only under exceptional conditions, gains access to the body at large, but multiplies locally at the seat of its introduction, it is clear that the disease must ultimately depend upon absorption of the toxin which is formed at the site of growth of the bacillus, and the action of that toxin upon the body. For in both diphtheria and tetanus, the symptoms of the disease point with unerring finger towards an implication of the central nervous system, which is far removed from the seat of growth of the bacilli in question. But the truth of this view is conclusively proved, when it is shown—and this can readily be done in both cases—that the disease in its entirety can be reproduced by introducing into the body the toxins formed by these bacilli apart from the bacilli themselves. It is therefore clear that certain micro-organisms are pathogenetic by virtue of the toxins which they produce, and it is highly probable that this is the chief way in which the greater number, if not all, pathogenetic bacteria act. But a glance at a microscopic section of the lung, spleen, or liver of a rabbit or guinea-pig that has succumbed to anthrax, in which suitable staining shows the capillaries to be literally packed with anthrax bacilli, leaves no doubt that a portion of the effect produced by that bacillus must be mechanical. Such a mechanical action is probably superadded upon the specific toxic action of all those bacteria which, at the time of death, are found to be swarming in the blood and organs. In the case of many hæmatozoal diseases, it is probable that mechanical action plays a most important part; whether the parasites form toxins or no, is unknown. Perhaps also, by consuming that nutriment which in the absence of the parasites would go towards supporting the cells of the body, they may in part act by leading to a condition which is akin to starvation.

(x.) **Specificity.**—In order to prove conclusively that a certain micro-organism is the cause of a certain specific disease, the following five fundamental conditions must be satisfied. The first four are known as "Koch's postulates."

I. The micro-organism must be found in the bodies of animals suffering from or dead of that disease, and that disease alone.

II. The micro-organism must be isolated from the body of the diseased animal, and must permit of pure cultivation in successive generations on artificial media outside the animal body.

III. A pure cultivation of the micro-organism thus obtained must, when introduced into the body of a healthy animal, reproduce the disease in question.

IV. In the second animal the same micro-organism must be found.

V. From this second animal it must be possible once more to obtain a pure cultivation of the micro-organism.[1]

Considering the stringency of the conditions imposed, and the youth of bacteriology as a science, it is astonishing how many micro-organisms have been already proved beyond question to be the causes of certain diseases.

From the nature of the case the number of diseases incidental to man, in which absolute proof has been given, is much smaller than in the case of diseases common to man and certain animals, or incidental to animals alone. With regard to the ætiology of most human diseases which are looked upon as of microbial origin, we are, however, at the present time forced to be content with evidence which, though in some cases it is almost conclusive, nevertheless does not amount to absolute proof. For other diseases (*e.g.*, syphilis, variola), though no micro-organism has as yet been discovered which can certainly be regarded as the cause, and though at present the only real evidence at our disposal is the infective nature of the disease, we may with confidence predict that at some future time they too will be classed amongst those diseases the causal relationship between each of which and a specific micro-organism has been scientifically proved.

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[1] This "postulate" is necessary in order to prove that the bacterium in question was in a living condition during the period in which the disease was running its course in the second animal: in other words, to prove that the disease in the second animal was the result of the vital activity of the micro-organism.

Below is given a list of the chief micro-organisms which are generally accepted to be associated with disease or diseased conditions in man.

| | | |
|---|---|---|
| Bacilli, . | *B. anthracis*, associated with | Anthrax, malignant pustule or wool-sorter's disease. |
| | *B. diphtheriæ*, „ | Diphtheria. |
| | *B. influenzæ*, „ | Influenza. |
| | *B. icteroides*, „ | Yellow fever. |
| | *B. lepræ*, „ | Leprosy. |
| | *B. mallei*, „ | Glanders. |
| | *B. œdematis maligni*, „ | Surgical gangrene. |
| | *B. pestis*, „ | Oriental plague. |
| | *B. pneumoniæ* (Friedländer), associated with | Some cases of croupous pneumonia, Rhinoscleroma (?). |
| | *B. pyocyaneus*, „ | Blue or green pus. |
| | *B. tetani*, „ | Tetanus. |
| | *B. tuberculosis*, „ | Tuberculosis in all its forms. |
| | *B. typhosus*,[1] „ | Enteric or typhoid fever. |
| Micrococci, | *Diplococcus gonorrhœæ*,[2] associated with . . . | Gonorrhœa, gonorrhœal conjunctivitis and gonorrhœal synovitis or rheumatism (?). |
| | *Diplococcus pneumoniæ* (Fränkel),[2] associated with | Most cases of croupous pneumonia; epidemic cerebro-spinal meningitis; some cases of otitis media; some cases of non-epidemic meningitis. |
| | *Staphylococcus pyogenes aureus* and *albus*, associated with . . . | Suppuration; septicæmia; pyæmia; osteomyelitis; endocarditis, simple and ulcerative. |
| | *Streptococcus pyogenes* (erysipelatis), associated with | Same conditions as those induced by *Staph. pyog. aureus*; erysipelas. |

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[1] This organism has also been found in pure culture in erysipelas.

[2] This organism has also been found in the heart-valves in ulcerative endocarditis.

| | | |
|---|---|---|
| Spirilla, | *Vibrio choleræ asiaticæ* (varieties of), associated with | Asiatic cholera. |
| | *Spirillum Obermeieri*, associated with | Relapsing fever. |
| True Moulds, | *Achorion Schönleinii*, associated with | Favus. |
| | *Actinomyces*, associated with | Actinomycosis; Madura foot (Kanthack). |
| | *Microsporon furfur*, associated with | Pityriasis ruber. |
| | *Trichophyton tonsurans*, associated with | Tinea tonsurans (ringworm). |
| Torula, | *Saccharomyces mycoderma*, associated with | Aphthæ (thrush). |

Below is given a list of infective diseases of which the specific micro-organisms have not as yet been certainly discovered, but concerning whose microbial[1] origin there is the strongest presumptive evidence:—

Coryza.
Follicular tonsillitis.
Morbilli.
Mumps.
Pertussis.
Rabies.
Rötheln.
Scarlatina.
Soft chancre.[2]
Summer diarrhœa.
Syphilis.
Typhus fever.
Varicella.
Variola and vaccinia.

In the following diseases incidental to man there is some reason for believing that a microbial[1] origin will in the future be discovered:—

Acute articular rheumatism.
Acute anterior poliomyelitis.
Chorea.
Landry's paralysis.
Rheumatoid arthritis.

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[1] Whether animal or vegetable it is of course impossible to say.

[2] This condition may depend upon some one or other of the pyogenetic cocci of particularly virulent type.

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# CHAPTER III.

## The Pathology of the Circulation—The Heart and Pericardium.

*Synopsis.*

I. Pathology of the Diseases of the Pericardium, direct and indirect.

II. Pathology of Endocarditis, direct and indirect.
    The Varieties of Endocarditis.
    The Effects of Valve Lesions on
        (*a*) The Sounds of the Heart. Murmurs.
        (*b*) The Size of the Cavities of the Heart.
        (*c*) The Thickness of the Walls of the Heart.
    The Effects of Valve Lesions on
        (*d*) Other Organs and Tissues of the Body.

III. Pathology of the Myocardium, direct and indirect. Stenosis of Coronary Artery.

IV. Pathology of Congenital Malformation of the Heart.

V. Pathological Variations of Cardiac Rhythm.
    Intermittence.
    Irregularity.

Though it will be convenient to divide the pathology of the heart and pericardium into sections according as the pericardium, the endocardium including the valves, the myocardium, the circulation of the heart, or the cardiac rhythm is more exclusively affected, yet it must clearly be stated that the importance of all these pathological conditions essentially depends upon the fact that they one and all induce changes in the heart itself whereby its function as the central force for the maintenance of the circulation becomes impaired. It will be found, therefore, that most of the conditions we are about to consider primarily affect the heart itself, and on that very account secondarily produce more or less grave affections of all other parts of the economy.

I. **Pathology of the Diseases of the Pericardium, direct and indirect.**—The pericardium may be the seat of a variety of changes, but by far the most common and important is inflammation or pericarditis. This may own many causes, *e.g.*, rheumatism, scarlatina, tuberculosis, renal disease, malignant disease; but the most usual form is that which supervenes during the course of acute rheumatism. Since the pathology of all these varieties is essentially the same, it will be sufficient to discuss pericarditis in general terms; such points as depend upon peculiarities in the particular cause we can ignore.

When the pericardium becomes inflamed the normal smoothness and glistening nature of the serous membrane becomes changed for a dull and lustreless appearance. At the same time, the blood-vessels which lie immediately beneath the endothelial covering of the membrane are seen to be engorged with blood. At first the membrane is dry, but by degrees inflammatory exudation from the blood-vessels makes its appearance and the membrane becomes covered by a more or less continuous and irregular layer of material, which, since it differs from normal blood-fibrin, has been called "lymph" or "plastic lymph." This material is structureless or consists of a fine meshwork of fibrils enclosing a variable number of leucocytes and such of the endothelial cells of the pericardium as may have desquamated. The amount of "lymph" present varies in different cases, being greater as the inflammation is more chronic. Owing to the fact that it is present on both visceral and parietal layers of the pericardium, the movements of the heart, so long as the layers are not separated by fluid, yield to the ear and even to the hand a characteristic "friction rub." A friction rub is of course most marked and most readily called out at that portion of the pericardium where the surfaces from their anatomical arrangement can be but little separated from one another, hence we find that it is earliest heard and persists longest about the roots of the great blood-vessels. Another region where it is frequently heard is at the seat of the cardiac impulse, for the apex of the heart with every systole brings visceral and parietal layers of the pericardium into contact at this point. Pericarditis in this stage is also accompanied by præcordial pain and rapid and weak heart action. These probably depend upon direct or indirect stimulation of the afferent nerve-fibrils which underlie the pericardium.

With regard to the pain, afferent impulses probably travel directly up to the higher parts of the brain, but the modified heart action probably depends on a partial removal of the normal tonic inhibitory action of the vagus, brought about on the one hand by stimulation of the augmentor nerves of the heart, and on the other hand by changes in the myocardium which always accompany pericarditis.

But the inflammation which leads to the formation of "lymph" leads, at the same time, to the exudation of fluid from the blood-vessels. If, as is invariably the case at first, the rate at which fluid is poured out exceeds the rate at which it is absorbed and carried away by the lymphatics, this fluid collects in the pericardial sac, and constitutes "pericardial effusion." According to the disproportion between exudation and absorption, *i.e.*, to the quantity of fluid in the pericardial sac, so are the effects upon the heart. Normally, the sac can hold a larger quantity of fluid than it at any given time contains, and therefore a certain accumulation of exuded fluid can be accommodated without stretching of the membrane. Instead of the layers—visceral and parietal—being in contact, they are now separated. Such an amount of exudation is eminently beneficial, for the inflamed surfaces no longer grate on one another with the heart's movements. Not only does this lead to a disappearance of the friction sounds, but also it relieves the patient of such symptoms as are due solely to the irritation of an inflamed serous surface. Unfortunately, the amount of exudation frequently exceeds such beneficial limits, and becoming pent up in the pericardial sac, produces a series of symptoms which are particularly distressing to the patient, and which can easily be shown to depend upon the intra-pericardial pressure.

If, in a dog, oil be injected into the pericardial cavity until the normal negative pressure is replaced by a positive pressure, and at the same time the blood-pressure be registered in one of the branches of the pulmonary artery, in the carotid, and in the external jugular vein, it will be found that the pressures indicated differ from the normal according to the amount of fluid injected into the pericardial sac. In the otherwise untouched animal the carotid pressure is about equal to that of 120 mm. of mercury, the pulmonary pressure equal to about 20 mm. of mercury, and the pressure in the external jugular vein is zero, or at most equals the pressure of a column of magnesium sulphate a few millimetres in height. If the amount of oil that is injected is small, such as, for example, would lead to a pressure of 20 millimetres of oil in the pericardial sac, the pressure in systemic and pulmonary arteries is seen to fall (the systemic pressure falling to the greater extent) and the venous pressure is seen to rise. Moreover, in the external jugular vein, pulsations synchronous with the auricular systole, and therefore presystolic so far as concerns the ventricular systole, make their appearance, though such pulsations were formerly absent, or at all events so little marked as to be almost invisible. If no more fluid be injected into the pericardial sac, the new levels of pressure become established and circulation goes on regularly; indeed, after a time, owing to relaxation of the pericardium, the pressure in the sac diminishes, and the arterial and venous pressures approximate more nearly to the normal. If, on the contrary, more oil is injected, the arterial pressures become lower and lower (the pulmonary pressure being extinguished first), and the venous pressure increases, until at last the systemic arterial pressure falls to zero. Under these conditions it is obvious that no blood at all enters the aorta, and the circulation of blood is at a standstill. That the results we have described are due to the pericardial pressure and not to any actual injury to the heart, can easily be shown by giving exit to the oil. Now, the heart contracts, the systemic and pulmonary arterial blood-pressures rise again to the normal, indeed for a time above the normal, and the venous pressure again sinks to zero.

The method whereby these modifications of the circulation are produced is as follows. The increase of pressure in the pericardial sac is an obstacle to the inflow of blood into the heart, for normally the inflow into the right auricle is greatly favoured by the difference in pressure outside and inside the thorax, or more strictly speaking, outside the thorax and inside the great veins at their entrance into the heart. Since the right auricle receives less blood than normal, it can pass on less blood to the right ventricle, the right ventricle in its turn ejecting less blood into the pulmonary artery; the pulmonary blood-pressure, therefore, falls. For the same reason, *i.e.*, because the pulmonary artery receives less blood than normal, less blood reaches the left auricle, and through it the left ventricle, by way of the pulmonary veins. Since the left ventricle receives less blood, its output into the aorta is diminished, and diminution of output of the left ventricle, unaccompanied as in this case by a corresponding increase in the peripheral resistance, is of necessity associated with fall of aortic blood-pressure.

The venous blood-pressure, on the other hand, rises, because with the injection of oil into the pericardial sac a new condition has been introduced into the circulation which disturbs the hitherto existing equilibrium between inflow into and outflow from the heart. It is evident, since the aortic blood-pressure is dependent upon the two factors, (*a*) output of the heart, and (*b*) peripheral resistance in the arteries, and since the output of the heart, *cæteris paribus*, depends entirely upon the inflow into the heart, that for the maintenance of a constant mean level of aortic blood-pressure the inflow into the heart and the output must be exactly equal. But the blood which constitutes the "inflow" is nothing more than that amount of blood which, as the result of their hyper-distension, passes from the arteries into the veins during cardiac diastole. In other words, for the maintenance of a constant aortic blood-pressure the amount of blood which passes from arteries to veins during a given cardiac diastole must be exactly equal to the amount of blood which has been thrown into the arteries during the previous cardiac systole, and *vice versa.*

Now, in the case of the dog before us, suddenly, as the result of the injection of oil into the pericardial sac, the output of the heart is diminished, but since, at the moment before this occurred, the hyper-distension of the arteries corresponded to a greater output, the amount of blood which passed from arteries to veins also corresponded to that greater output. More blood, therefore, leaves the arterial system during any given diastole than enters it during the succeeding systole; an additional amount of blood, therefore, becomes stored up in the veins with each heart's diastole until equilibrium is once more established, gradually leading to the rise in venous pressure which we have noted.

It is this rise of venous pressure which renders maintenance of the circulation possible under the altered conditions, for it is obvious that if the pericardial pressure were by the injection of oil raised to, say, 25 mm. of oil, while the pressure in the external jugular and other veins outside the thorax remained at their normal point, no blood would flow into the right auricle at all, and the circulation would immediately cease. As it is, however, the venous pressure rises with the intra-pericardial pressure and always maintains a slight superiority; blood, therefore, flows into the right auricle, and though the pressures in arteries and veins are altered, the circulation goes on. But the pressure which can be attained in the venous system has a limit which varies with many factors, but which is in the majority of dogs equal to that of about 280 or 300 millimetres of magnesium sulphate. So long as the intra-pericardial pressure is below this, the circulation continues, however poorly, but once the intra-pericardial pressure reaches this point, all possibility of inflow from veins to auricle ceases, and circulation comes to a standstill with the whole of the blood of the body collected in the veins. The heart, however, for a minute or thereabouts continues to contract, and if during this time the intra-pericardial pressure be reduced, circulation re-establishes itself as has already been said.

Now in cases in which a considerable pericardial effusion has taken place, whatever be its cause, the symptoms that are produced are essentially the same as those which have been seen to occur after the intra-pericardial pressure in the dog has been increased by injection of oil into the pericardial sac, for the patient's pulse is small and weak, and the veins in the neck are engorged and pulsate. But in addition to these symptoms others are present which cannot be so well discovered in the dog, but the dependence of which on the pericardial condition is no less clear. The area of cardiac dulness is increased, for the distended pericardium pushes away the lungs on both sides; moreover, the outlines of the dulness, though widened by yielding of the pericardium under the pressure, correspond closely to the normal pear-shaped outline of that membrane. The patient is livid or "cyanosed," and the cyanosis depends upon non-aëration of the blood. This has a twofold origin: firstly, the amount of blood which passes through the lungs at each heart's beat is greatly diminished, and secondly, the period during which the blood remains in the systemic capillaries is increased as the result of the closer approximation of arterial and venous pressures, and therefore a greater length of time is afforded for the removal of oxygen from any particular portion of blood by the tissues.[1] Lastly, the identity of the effects of increase of pericardial pressure under the two conditions, pathological and experimental, is conclusively proved when it is added that in the patient, as in the dog, all pressure-symptoms disappear when exit is given to the pericardial fluid.

The amount of fluid that is necessary to bring about such a condition as we have been considering is by no means constant, for if the increase of intra-pericardial pressure be brought about gradually, the pericardium yields to a considerable extent, and a larger collection of fluid is necessary to produce the same severity of symptoms as would be produced by a smaller quantity of fluid if the filling of the pericardium occurred rapidly. This is very well seen by comparing the results of rupture of an intra-pericardial aneurism, or rupture of the heart-wall, with the results of an effusion occurring in such a condition as chronic valvular disease. In the latter case, the amount of fluid may reach to as much as three pints, and yet the patient may not be conscious of very severe distress, for the accumulation of fluid has been going on for days; but with rupture of the heart or with bursting of an intra-pericardial aneurism, though the amount of blood poured out may not exceed 150–200 c.c., yet death occurs within a few minutes. Moreover, it is not by reason of its property of coagulation that the blood in these latter cases acts, for fatal results occur in the same way when a large hydatid cyst of the liver ruptures and discharges its non-coagulating fluid into the pericardial sac. In those rare cases in which the fluid in the pericardium becomes purulent, the symptoms, though aggravated by cardiac changes induced by absorption of toxic substances from the pus, are otherwise identical.

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[1] Orthopnœa, another symptom which shows itself, will be considered along with the Pathology of Respiration.

But a pericardial effusion does not invariably end fatally or call for surgical relief (paracentesis); in the majority of cases of pericarditis, and pericarditis is by no means uncommon where acute articular rheumatism is present, the effusion, after causing some distress, becomes absorbed by the lymphatics. This occurs at a varying time after the original onset of the pericarditis and leads to two chief results. In the first place, with the removal of the fluid the area of præcordial dulness diminishes and the two roughened pericardial surfaces again come into contact, producing a reappearance of the friction rub. In the second place, the "lymph" becomes "organised," *i.e.*, it becomes converted into fibrous tissue.

**Adherent Pericardium.**—The organisation of the "lymph" leads to different results in different cases; in one, a thickened and fibrous pericardium may result, but the visceral and parietal layers still enclose a space; in another, adhesion may take place between portions of the visceral and parietal layers, and fibrous cords or bands may connect them, or even the appearance of a loculated sac may be presented; in yet a third, the two layers of the pericardium may be closely adherent throughout their whole extent, so that the former cavity of the pericardium is completely obliterated. The effects produced by these different terminations differ in degree, but they all coincide in the fact that they throw extra work upon the heart, which now has to contract against an additional resistance besides the normal resistance in the arteries. We shall see later that, within limits, if increased work is demanded from any muscle, it hypertrophies. The heart is no exception to this rule; an adherent or partially adherent pericardium causes hypertrophy of the ventricular walls.

But an adherent pericardium leads to other secondary results.

Owing to the artificial rigidity which is thereby given to the walls of the heart, they are unable to contract in a normal manner, and one of the most important effects of the condition is that the normal closure of the different valves of the heart is interfered with to a greater or less extent, and circulatory disturbances are set up. Since these disturbances are essentially similar to those which result from endocarditis, they need not further be noticed here, but they must be borne well in mind. If, as is sometimes the case, lime salts are deposited in the newly formed fibrous tissue of the adherent pericardium, the obstacle to the circulation is still further increased.

II. **The Pathology of Endocarditis, direct and indirect.**—The causes which lead to pericarditis even more commonly induce endocarditis; this condition may therefore occur in association with pericarditis or may be independent of it. When endocarditis is acute it is always clearly secondary to some other disease, or at all events is associated with pathological lesions in other parts; but some of the chronic forms—namely, those in which the endocardium has not obviously been the seat of antecedent acute inflammation—are, in a sense, primary. These non-inflammatory forms of endocarditis[1] have their counterpart in the "milk-spots" which are often to be found on the visceral pericardium, and which are certainly independent of antecedent inflammation. In the endocardium, non-inflammatory fibrosis is of great importance, from the fact that it often attacks the valves; indeed, in all cases, affections of the endocardium and valvular disease are almost synonymous terms.

The valves of the heart are not equally liable to disease, for though diseases of the aortic and mitral valves are common, diseases of the pulmonary and tricuspid valves are rare, and in most cases congenital. It must not be supposed, however, that the right side of the heart does not suffer when the valves on the left side are affected, for such is not the case; on the contrary, the troubles of which the patient with aortic or mitral disease complains are very largely due to failure not of the left but of the right heart.

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[1] Since the termination "itis" in Pathology is used to designate "inflammation" (bronchitis, arthritis, etc.), the expression "non-inflammatory endocarditis" is a contradiction in terms. It will be shown later that it is very doubtful whether many of the so-called "chronic inflammations" have any right to be classed as "inflammatory" at all. The term is here used only in deference to custom.

When, in the course of some acute disease such as acute rheumatism, any of the valves of the heart are affected, they are seen, if examined sufficiently early, to present on their auricular surfaces, *i.e.*, those which are directed towards the main current of the blood-stream, a number of small, greyish, semi-translucent elevations, each of which is about the size of a pin's head. These elevations or "granulations" are situated at a short distance from the free edges of the flaps of the valve, and form lines which, on bringing the flaps into the normal systolic position, are seen to coincide with the lines of junction of the flaps during ventricular systole. If a granulation be examined at this early stage it is found to be composed of a mass of proliferated endothelial cells, but it does not remain such for long; degenerative processes set in, some of the endothelial cells are cast off, and a roughened surface is presented to the blood-stream, upon which, in the natural order of events, fibrin is deposited. Hence the granulations of early endocarditis, as seen in the post-mortem theatre, usually consist of small masses of endothelial cells capped with fibrin.

The fact that the lines of granulations on the cusps of the valve are opposite to one another, and are directly in contact during ventricular systole, suggests that direct infection may play a prominent part in their formation, while their relation to the blood-stream suggests that their *causa causans* is circulating with the blood. In support of this view, we find that, immediately beneath the cap of fibrin and in its deepest layers, masses of staphylococci or streptococci may generally be demonstrated by appropriate staining. The complete formation—proliferated endothelial cells, micro-organisms, fibrin—is frequently termed a "vegetation."

The mode in which granulations are formed may be looked at in two ways: either (*a*) cocci circulating in the blood attach themselves at some one point of the valve and there grow, infecting the rest of the cusp and adjacent cusps directly by continuity or approximation of tissue; or (*b*) the blood is modified by the presence in it of some soluble deleterious substance (microbial toxin?) or in some other way, and the modified blood acts as an aseptic irritant to the endocardium, particularly at those points which are most exposed to the effects of pressure or to slight injury, viz., the lines of contact of the flaps. In the latter case the micro-organisms which are so frequently present must be regarded as secondary, and as having been deposited from the blood in a region of diminished resistance. At the present time, it is impossible to decide between these two views owing to the difficulty of obtaining specimens of granulations prior to the deposition upon them of fibrin from the blood.

**The Varieties of Endocarditis.**—Two varieties of acute endocarditis are recognised by physicians: (*a*) simple, and (*b*) ulcerative (also known as malignant or infective). Though these two varieties differ in their clinical aspects to such a degree that their separation in the wards is necessary, yet pathologically it must clearly be recognised that the two varieties are but more or less marked examples of the same process. It is true that in ulcerative or infective endocarditis micro-organisms are almost invariably found in the vegetations on the cardiac valves, but, as we have seen, they are very commonly present in cases of what would be termed simple valvulitis. Nor can any difference be established between the kind of micro-organism found in the two varieties. In both usually *Staphylococcus pyogenes aureus* is present; nevertheless, in the ulcerative form *Streptococcus pyogenes*, *Diplococcus gonorrhœæ*, *Diplococcus pneumoniæ* have been found.

Apart from the fact that ulcerative endocarditis is generally superposed upon a pre-existing simple endocarditis, the main difference between the varieties lies in the degree of virulence of the micro-organism present. In simple endocarditis they act as irritants and lead to an inflammation which ends in repair; in ulcerative endocarditis they act as irritants and lead to an inflammation which ends in necrosis. This difference in virulence of the micro-organisms shows itself throughout the whole clinical histories of the two conditions. The ulcerative form with its hectic, rigors, sweats, is severe primarily because a large amount of the toxins which cause those symptoms is produced; the simple variety is less severe because such toxins are not produced or are produced only in quantities that can be dealt with by the body without great distress. In both varieties portions of the fibrinous vegetations may be broken off and carried in the blood-stream to distant parts as "emboli," but whereas in simple endocarditis the emboli are aseptic or contain only attenuated micro-organisms, in ulcerative endocarditis the emboli are septic and the micro-organisms they carry produce at the seat of their arrest changes identical with those which are occurring in the valves, *i.e.*, ulceration, necrosis, and pus-formation. Further, the effects of the two varieties of endocarditis upon the heart as the central factor in the circulation are identical in kind though they differ in degree, for though the amount of destruction of valve substance and the amount of fibrin deposit are so much greater in the case of ulcerative endocarditis as to be almost pathognomonic, yet destruction of valve substance and deposit of fibrin also occur in simple endocarditis. Lastly, with regard to the heart muscle itself, it is true, though perhaps not so evident at first sight, that the two varieties of endocarditis differ not in kind but only in degree. Both forms cause modification of the myocardium, but whereas the simple variety causes, first, impairment of function, and later an improvement from that impaired condition, the ulcerative variety, mainly from the effects of toxic action, causes impairment of function throughout, so that to a greater degree of impairment of valve is added a greater degree of impairment of muscular power of the heart, and that too at a time when extra demands are being made upon it. It is seen, therefore, that, pathologically, simple and ulcerative endocarditis differ only in degree, and that such differences as characterise the two clinical varieties depend solely upon the virulence of the micro-organisms present, or, in other words, upon the amount of toxin which those micro-organisms produce.

Besides the acute varieties of endocarditis, the valves of the heart are prone to undergo changes which lead to thickening and puckering of their free edges, adhesion of adjacent parts of separate flaps, etc. These changes are essentially chronic and of a fibrotic type; if advanced, the cusps of the valve may become irregular in outline, and almost cartilaginous in hardness. In many cases lime salts are deposited in the modified tissue, and thus motility of the valves may be completely abolished. Changes such as these are particularly liable to produce "stenosis" or narrowing of the valvular orifice; as examples may be given mitral stenosis leading to a so-called "button-hole mitral orifice," and aortic stenosis in which the entrance to the aorta may be a mere irregular chink with completely immovable edges. In some cases, no doubt, these chronic changes are of inflammatory nature, and are due to repair of valves that have at a previous time been the seat of acute simple endocarditis, but in many cases diseases leading to acute valvulitis (*e.g.*, acute rheumatism) have not been antecedent, and, as we have said, there is reason to believe that many of the so-called chronic forms of endocarditis are not inflammatory at all in the usual acceptance of the term. In the case of aortic disease of the chronic type, at all events, syphilis and old age seem to be important predisposing causes, and the change in the valves bears a much closer resemblance to atheroma or to simple fibrosis than to inflammation. As a matter of fact, the explanation of fibrosis and of calcification in the valves of the heart is as obscure as is the explanation of those same processes when they occur elsewhere in the body.

We have briefly considered above the direct effects of endocarditis so far as they concern the heart-valves themselves; the effects of such valve lesions (and we may add to them valve lesions produced by injury, such as rupture of the flaps or of the chordæ tendineæ) upon the heart itself and upon the body at large must now be examined.

In the first place, it is evident that a valve lesion may act primarily in either of two ways: it may (*a*) impede the flow of blood through an orifice by leading to narrowing or stenosis of that orifice, and this obstruction to the flow of blood will act during the systole of the cavity behind[1] the stenosed orifice; or (*b*) it may, by interference with the closure of the valves, allow of reflux through an orifice during *systole* of a ventricle if that orifice be either mitral or tricuspid, or during *diastole* of a ventricle if that orifice be either at the aortic or the pulmonary semilunar valves. Valvular disease may therefore be either "obstructive" or "regurgitant," a valve may be either "stenosed" or "incompetent." As a rule, when obstruction is present, it is accompanied by a greater or less degree of regurgitation, but the converse is not true, for uncomplicated regurgitation is frequently seen.

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[1] *I.e.*, with reference to the direction of the normal blood flow.

Obstruction or regurgitation may occur at any of the valvular orifices of the heart, but relatively uncomplicated obstruction is far more common at the mitral than at the aortic orifice, while on the right side of the heart a variable but usually small degree of obstruction at the pulmonary semilunar valves is the commonest form of all the varieties of congenital heart disease. Beyond this broad statement little more can be said as to the relative frequency with which the various orifices of the heart are affected, owing to the fact that other valves besides the one primarily affected become of necessity secondarily involved, if the patient lives for a sufficient length of time. It may, however, be added that aortic disease is commoner in men than in women, and that lesions of the mitral valve (especially mitral stenosis) are commoner in women than in men.

With regard to their gravity there is a general consensus of opinion that obstruction is less grave than regurgitation, and that mitral regurgitation is less grave than aortic regurgitation. Valve lesions of the left heart may therefore be arranged in the following order of severity, beginning with the least severe: 1, aortic stenosis; 2, mitral stenosis; 3, mitral incompetence; 4, aortic incompetence. On the right side of the heart a moderate degree of stenosis of the pulmonary orifice is of but little import; tricuspid regurgitation, on the other hand, especially if secondary to a valvular lesion on the left side, constitutes one of the most severe forms of disease to which the heart is liable. Tricuspid stenosis and pulmonary regurgitation are so rare as to be almost unknown.

The effects of valve lesions show themselves upon (A) the sounds of the heart, (B) the size of the cavities of the heart, (C) the thickness of the muscular walls of the heart, (D) other organs and tissues of the body. Each of these must be considered somewhat in detail.

**A. The effects of Valve Lesions upon the Sounds of the Heart.**—Though it cannot be said to be a matter beyond doubt in the case of the first sound it is probable that this is largely, and it is certain that the second sound is entirely of valvular origin; it is therefore only reasonable to expect that any modification of the valves should lead to corresponding changes in either the first or the second heart sound.

*Aortic Valves.*—If there be *obstruction* at the aortic orifice, the effect of that obstruction will be to introduce some modification of sound during that period of the cardiac cycle when the blood is passing the obstruction, *i.e.*, during ventricular systole. We shall therefore find that the first sound of the heart as heard at the base is replaced by a more or less rough or harsh sound[1] which is best heard in the second costal interspace on the right side, as being that point where the aorta comes most closely in relation with the chest wall, but which may also be heard over the carotid arteries, or even over the femoral arteries, at points where these vessels are superficial. If there be *regurgitation* at the aortic orifice, the modification of heart sound will take place during ventricular diastole; the normal sharp and clear second sound will be abolished or modified, and a murmur will be heard during a longer or shorter portion of the diastole. This murmur may be loudest either at the base of the heart, or, owing to the superior conducting power of the sternum, along that bone, but in most cases it is heard best at the ensiform cartilage. The exact explanation of the fact that an aortic regurgitant murmur is frequently best heard at the ensiform cartilage is not quite clear, but it probably depends upon the fact that the sound formed at the aortic orifice is conducted by the septum and by the regurgitant column of blood towards the apex, but in the main is transferred by the right ventricle and the blood which it contains to the sternum at the lower end.

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[1] In cases where there is extreme aortic stenosis due to calcification of the aortic semilunar valves the murmur may have a cooing or a musical character, but it is not proposed to discuss the varieties of abnormal heart sounds at length.

At first sight, one might suppose that the sound, if conducted by the septum and the regurgitant column of blood towards the apex, should be heard best at the seat of cardiac impulse, since that is the point where the septum and the regurgitant column of blood come most closely in contact with the chest wall; but it must be remembered that the apex of the heart only comes into contact with the chest wall during ventricular systole, *i.e.*, during that especial portion of the cardiac cycle when the aortic diastolic murmur ceases. Nevertheless, in a few cases, aortic regurgitant murmurs are best heard at the seat of cardiac impulse.

*Mitral Valve.*—If the mitral valve allow of *regurgitation*, the normal first sound of the heart is in whole or in part replaced by a systolic murmur. This systolic murmur is best heard at the apex, may be traced round into the left axillary region, and occasionally may be heard at the angle of the left scapula. It is best heard at the apex, because ventricular systole, during which the sound is being produced, brings the apex of the heart into contact with the chest wall, and therefore at the seat of cardiac impulse one's ear is in the most intimate relation with the seat of production of the sound. It is conducted into the axillary region by continuity of tissue, for during the period of formation of the murmur the heart's apex is in contact with the chest wall, and a portion of the vibrations which cause the murmur is conducted still in the same direction (a line joining auriculo-ventricular orifice and apex produced in the latter direction) by the thoracic wall. It is heard at the angle of the scapula, because a portion of the sound formed at the mitral orifice is conducted directly backwards by the solid tissues (descending aorta, root of lung, etc.), which lie between the seat of production of the sound and the chest wall in this direction. If mitral *stenosis* be present, a murmur is formed in the neighbourhood of the mitral orifice and is conducted to the apex, where it is well heard and usually strictly localised. As to the time at which this murmur is audible with reference to ventricular systole, there is some difference of opinion; most authors regard it as being formed during auricular systole and as due to obstruction of the flow of blood from left auricle to left ventricle—they therefore speak of it as "presystolic"; other authors (Charlewood Turner, Dickinson, and others) maintain that it is audible at the moment of cardiac impulse, that it is therefore in reality systolic, and is formed by regurgitation through a contracted mitral valve. The point is one which it is very difficult to decide, even with most careful auscultation; the fact, however, that the murmur in question is best heard at the region of cardiac impulse seems to suggest that it is formed during the period of the cardiac cycle, when the apex of the heart is in contact with the chest wall, *i.e.*, during ventricular systole. But why, if that be the case, the murmur should have its strict localisation and should present so marked a contrast to the ordinary mitral systolic murmur, it is difficult to say. This is of the less importance, since it is agreed on all hands that the murmur in question, whether it is to be regarded as systolic or as presystolic, is always associated with stenosis of the mitral valve.

*Pulmonary and Tricuspid Valves.*—On the right side of the heart, if obstruction be present at the orifice of the pulmonary artery, the normal sound formed at this point is replaced by a more or less harsh murmur heard in the second left costal interspace, which is the point where the pulmonary artery, or rather its left branch, is in closest relation with the chest wall. Lesions of the tricuspid valve rarely produce any specific murmurs, partly by reason of the depth at which the valve is situated in the thorax, partly by reason of the absence of good conducting material, and partly by reason of the small force with which the right ventricle contracts. Occasionally, in tricuspid regurgitation, a systolic murmur formed in the neighbourhood of the tricuspid valve may be heard in the fifth right costal interspace three and a half inches to the right of the sternal border.

*Physics of Murmur-Formation.*—As to the mechanism of murmur-formation it was long held with Laennec that murmurs are formed by the passage of blood over a roughened surface, but the facts that cardiac murmurs may be heard with great distinctness when the autopsy reveals perfectly healthy valves, and that in anæmia intensely loud murmurs may be heard in the veins of the neck when those veins are in no way diseased, are alone sufficient to negative this view. But, in addition, though the cavity of an aneurism is markedly rough, the production of a murmur over an aneurism is by no means invariable.

At the present time, it is generally held that murmurs are formed by the passage of fluid from a narrower into a wider cavity. If a bulb be blown on a piece of ordinary glass tubing which is provided with a T-piece, and water be allowed to flow from a reservoir through the bulb (the T-piece being situate between bulb and reservoir), nothing remarkable will be observed; but if, at the same time, through the T-piece a small constant stream of coloured fluid be allowed to flow, it will be noticed that though the coloured stream remains distinct from the water for some little distance after entering the bulb, yet it forms eddies in the bulb itself before becoming completely mixed with the water. It is assumed that similar eddies are formed when the blood passes any narrow opening (such as those which cause stenosis or allow of regurgitation) into a wider space beyond, and that the eddies thus formed on the distal side of the constriction produce vibrations of the vessel or heart wall which are conducted to the ear as audible sounds, and constitute the murmurs.

But this does not constitute the whole explanation. It is certain that the "*bruit de diable*" heard in the veins of the neck in anæmia may be intensified by exerting slight pressure on the neck with the stethoscope, but a *bruit de diable* is not generally brought out in a healthy person however much pressure be applied. The ease with which eddies are formed depends principally upon the degree of constriction as compared with the diameter of the cavity beyond the constriction, but depends also upon the velocity of the flow and upon the viscosity of the fluid, varying directly with the first and second, inversely with the third. In anæmia, since the specific gravity of the blood is markedly lower than normal, there is reason to believe that the viscosity of the blood is diminished, and it may be that in this lies the true explanation of anæmic and many of the so-called functional murmurs.

The fact that the readiness with which eddies are formed varies directly as the velocity with which the fluid is moving, affords an explanation of certain well-known peculiarities of murmurs.

Thus, a soft murmur is often associated with a weak heart, and may give place to a loud murmur when, under the influence of rest or drugs, the myocardium has become strengthened and capable of ejecting the blood with a greater degree of force. Again, a murmur which is absent or is inaudible when the patient is in the recumbent position, may be distinctly audible when the patient is placed in the sitting or standing posture, or if he have just taken a few steps up and down the room. Under any of these conditions the heart contracts more rapidly and more forcibly than when the patient is in the recumbent position, and the result is that the velocity of the blood-stream is increased. Again, the disappearance of a murmur when organic disease of the heart is known to exist is frequently of grave import, meaning, as it may do, that the muscular force of the heart has become impaired to such an extent that it can no longer impart sufficient velocity to the blood for the formation of murmurs. Speaking broadly, therefore, it may be stated that if organic disease of the valves or myocardium be present, a loud murmur is of less serious import than a soft murmur, and this because a loud murmur generally implies that cardiac contraction is taking place with some considerable amount of force. Murmurs occurring in the absence of recognised organic disease of valves or myocardium fall into quite a different category of case, though of course their mode of formation must be identical. We shall consider them along with functional diseases of the heart.

B. **The effect of Valvular Lesions upon the Size of the Cavities of the Heart.**—With regard to this point, it will be necessary to consider the ventricles more closely than the auricles. Owing to the fact that the left auricle is in connection with the large pulmonary venous system, which is unprovided with valves, the pulmonary veins and the left auricle may be regarded as forming part of one large cavity with thin walls extending between the pulmonary semilunar valves and the mitral valve: the right auricle similarly forms another large thin-walled cavity, owing to its connection with the superior and inferior venæ cavæ. The ventricles, on the other hand, though their walls are thick, form small cavities bounded by the auriculo-ventricular and the semilunar valves.

If the quantity of blood in any of the cavities of the heart (the auricles being considered here anatomically) be increased, the effect that such an increase has upon the size of the cavity depends entirely upon the cavity in which the increased volume of blood is situated. If, for example, the volume of blood in the left *auricle* be doubled, the increase of pressure which that increase of volume of blood produces, immediately reacts throughout the whole of the large pulmonary venous system, and a minute passive distension of that system readily affords room for the few extra cubic centimetres of blood: the size of the left auricular cavity remains practically unchanged. But if the volume of blood in the left *ventricle* be doubled, the only manner in which that blood can be accommodated along with competency of the valves, is by a distension or dilatation of the ventricular cavity. It follows, therefore, that increase in the amount of blood which is contained in the heart at any given time produces a far greater effect upon the size of the ventricular than it does upon the size of the auricular cavities.

Now it may readily be shown that one of the earliest effects of a valvular lesion is to increase the volume of the residual blood.[1] If we assume that aortic stenosis be suddenly produced in a given ventricular systole at the moment when the mitral valve closes, and that the effective force and duration of the systole remain constant, it is clear that at the end of that systole a larger amount of blood must remain in the left ventricle than remained at the end of previous systoles; for the force of propulsion and the time remain constant, but the diameter of the outlet is diminished. But during the period between closure of the mitral valve in this first systole after production of aortic stenosis, and its subsequent opening, the amount of blood which has collected behind the mitral valve and the pressure which that blood exerts, are the same as when the aorta was unobstructed. Hence, at the commencement of the second systole after the production of stenosis, the left ventricle not only has to find room for that amount of blood which it was unable to pass into the aorta at the last systole, but also for an amount corresponding to a *normal* ventricular output, and reaching it from the left auricle. It must therefore dilate, and it will continue to dilate with each diastole until the amount of blood which it receives during diastole is equal to the amount of blood which it ejects into the aorta during systole. If, now, no further modification be introduced, the *status quo* will be maintained and the circulation will go on, but the quantity of residual blood remaining in the left ventricle at each systole, though constant, will be greater than normal, and the left ventricle itself will be dilated. In the same way obstruction at the pulmonary semilunar valves leads to dilatation of the right ventricle, but since the walls of the right ventricle are thinner than those of the left, it is less able to withstand increase of pressure, and therefore yields more readily to dilating forces.

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[1] By the term "residual blood" is meant that quantity which either ventricle contains at the height of systole.

If, instead of obstruction, regurgitation takes place, the same dilatation of the ventricles must also occur. In the case of aortic regurgitation it is evident that the amount of blood which the left ventricle is called upon to contain must be largely increased, for the whole of the arterial peripheral resistance is tending to force the blood back from the systemic arteries into the left ventricle during its diastole. But the same is true if regurgitation occurs at the mitral valve, for the left ventricle during its diastole is obliged to receive not only an amount of blood equal to the volume which at its last systole it injected into the aorta, but also that additional amount which during the preceding systole it had forced back into the left auricle instead of onwards into the aorta. Moreover, in this case the regurgitant column of blood raises the pulmonary venous pressure and thereby increases one of the forces which are about to produce ventricular dilatation in the succeeding diastole. *Mutatis mutandis*, the same is true in the case of tricuspid incompetence.

C. **The effects of Valvular Lesions upon the thickness of the Muscular Walls of the Heart.**—It has been stated above that if the effective force and duration of the ventricular systole remain constant, but the diameter of the aortic orifice be diminished, the amount of residual blood in the left ventricle increases, and, therefore, the cavity dilates. This statement tacitly includes another factor which comes into play when any valve of the heart becomes diseased. In the case of a contractile sphere with liquid contents (and the ventricle filled with blood may be regarded in this light), dilatation produces two results: 1, the walls become thinner, and 2, as Roy and Adami have pointed out, the resistance to contraction of the wall is increased. Now it follows from these considerations that the *effective* force of the ventricle cannot remain constant when dilatation is occurring, unless the *actual* force of ventricular contraction increases. It is to this latter point that attention must now be turned.

The effect that will be produced upon the muscular walls of the heart by any valvular lesion depends chiefly upon three main factors: 1, the initial nutritive condition of the muscular tissue of the heart; 2, the amount of circulatory disturbance that the valvular lesion itself introduces; and 3, the situation of the valve that is affected. The first we shall discuss along with the pathology of the myocardium; it need here only be remarked that unless the muscular tissue be healthy none of the changes we are about to detail can take place, or only to a limited extent. With regard to the amount of circulatory disturbance introduced by the valvular lesion itself, it is clear that the lesion may be so suddenly produced or may be so extensive that the dilatation of the ventricles to accommodate the increase of residual blood proceeds by strides so great that the normal reserve power of the ventricle, though exerted to the full, is unable to maintain a constant effective force of systole. Under these circumstances ventricular dilatation must lead through the series of stages which constitute " cardiac failure " and must end in death. At the autopsy the heart muscle will be found flabby and thinned, the ventricles dilated, and both they and the auricles distended with blood; the picture will be one of a heart that has completely failed to cope with its contents.

Fortunately, however, such a termination is comparatively rare. More commonly the amount of dilatation that is produced by the valvular lesion is sufficiently small for an effective systole to be brought about by a call upon the reserve power of the heart which can be met; sudden and fatal dilatation of the ventricle is thereby staved off. But since the dilatation of the ventricles increases the resistance to contraction, whereby more work is thrown upon the muscular walls of the heart, the heart muscle responds in the manner customary with all muscular tissue when it is intermittently[1] called upon to perform more work and hypertrophies. The ventricular wall becomes again as thick as it was before dilatation set in, or even thicker, the heart beats with increased force, and the cardiac impulse may be "heaving" in character.

At the same time, since the left is the chief ventricle to undergo change, the apex of the heart becomes displaced downwards and outwards, and the visible impulse may be in the seventh costal interspace well to the outer side of the nipple line. Along with the onset of hypertrophy, need for assistance from the reserve force of the heart ceases, and since the hypertrophied heart under the conditions we are considering produces a more powerful systole, a greater amount of blood than is received by the ventricle is, for a time, ejected by it at each heart's beat into the aorta. The amount of residual blood is thereby diminished and *pari passu* the cavity of the ventricle tends to return to its original normal size. The natural cure, therefore, for dilatation of the heart is the muscular hypertrophy which that dilatation induces.

We have spoken throughout chiefly of the left ventricle, but the right ventricle also undergoes identical changes when there is obstruction to the flow of blood through the pulmonary orifice, or when the tricuspid valve becomes incompetent. Nevertheless, there are certain differences which must be noted with reference to this cavity. In the first place, changes in the right ventricle *dependent upon valvular lesion* are, with the exception of the rare cases of primary valvular disease of the right side of the heart, always immediately preceded by mitral incompetence. As the result of this mitral incompetence, the blood pressure in the pulmonary venous system is raised, for at each systole of the left ventricle blood regurgitates through the mitral orifice into the left auricle, which is in direct continuity with the pulmonary veins. This increase of pulmonary venous pressure acts backwards through the pulmonary capillaries upon the blood in the pulmonary artery and creates an obstacle to the opening of the pulmonary semilunar valves. More work is therefore thrown upon the right ventricle, which, following the law we have discussed above, dilates to accommodate an increase of residual blood, and also hypertrophies. In the second place, owing to the thinness of the right ventricular wall, accumulation of residual blood more readily leads to dilatation on this side of the heart than it does on the left side. One may, therefore, briefly state that while dilatation and hypertrophy occur in the case of both ventricles as the result of valvular lesion, dilatation is more common and more marked in the right ventricle, hypertrophy is more common and more marked in the left ventricle.

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[1] It will be seen later that intermittence of action of a stimulus is essential to the occurrence of hypertrophy.

To the more common hypertrophy of the left ventricle also conduces the fact that lesions of the aortic and mitral valves are so much more frequently met with than lesions of any other valves. Aortic stenosis throws more work upon the left ventricle, for though the volume of blood to be injected into the aorta is the same, the duration of systole is not increased[1] and the aortic orifice is diminished in diameter. In the cases of aortic regurgitation and mitral regurgitation, more work is demanded of the left ventricle, because, in the first case, it not only has to inject into the aorta the normal amount of blood but also that amount which has returned to it during the preceding diastole, and in the second case, because it is necessary, if the volume of blood injected into the aorta is to remain normal, that the volume of blood upon which the left ventricle contracts should be greater than normal by an amount equal to that amount which is destined to return into the left auricle by regurgitation.

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[1] It is not absolutely correct to say that the volume of blood to be injected into the aorta and the duration of systole remain normal when the aortic orifice is stenosed. The atrophic condition of parts supplied by systemic arteries in many cases is clear evidence that such parts do not receive their full blood supply. With regard to the duration of systole, the matter is more difficult; owing to the larger area of heart which comes into contact with the chest wall during systole an impression is given of a prolonged systole. According to Fagge and Pye-Smith, the pulse in aortic stenosis is infrequent, but infrequency of pulse must be regarded as evidence of prolongation of diastole rather than as evidence of prolongation of systole; and though the sphygmograph shows that with extreme stenosis the summit of the pulse-wave is more slowly reached than normal, great caution must be exercised in interpreting cardiac events by the light of sphygmographic tracings. In any case the statements made in the text do not err largely.

In aortic stenosis and regurgitation the dilated and hypertrophied heart may weigh as much as forty-five ounces (Fagge and Pye-Smith).

Mitral stenosis, it is generally asserted, leads to hypertrophy of the left auricle by reason of the increased work that is thrown upon the walls of that cavity in their endeavour to pass the blood through the contracted mitral orifice. In many cases, no doubt, the auricular wall is thicker than normal, but a far more constant change in mitral stenosis is a moderate amount of hypertrophy with dilatation of the left ventricle. It is on this fact that those authors largely rely who maintain that the essential circulatory disturbance produced by mitral stenosis is regurgitation. They hold, with justice, that the hypertrophy and dilatation indicate increased work, and that it is difficult to see how increased work can be thrown upon the left ventricle if the only or the chief result of mitral stenosis is to diminish the amount of blood entering that cavity. If such were the case, the left ventricle should be not dilated but contracted, and its walls should be not hypertrophied but atrophied.

Dilatation and hypertrophy of the ventricles have been dealt with separately for the object of clearness, and it has been shown that, theoretically, dilatation of the heart must precede hypertrophy, when both are the results of a valvular lesion. Pathologically, however, they accompany one another, and a heart that is hypertrophied is almost invariably dilated. The converse, that a dilated heart is almost invariably hypertrophied, is not true; for if from any cause the nutritive condition of the muscular tissue is impaired, or if the valvular lesion be very severe or of very sudden onset, hypertrophy may fail completely and dilatation alone may be found. Nor do hypertrophy and dilatation run hand in hand. In a favourable case, at first hypertrophy outstrips dilatation, but in all cases of valvular lesion, however favourable at first, if the disease proceeds to its natural termination, hypertrophy fails more and more to keep pace with dilatation as time goes on, and at last dilatation goes to the front and rapidly brings about death of the patient.

D. **The effects of Valvular Lesions upon other Organs and Tissues of the Body.**—If the overwhelming importance of the heart in the economy, and its dependence upon integrity of valves for the due performance of its functions, be borne in mind, it is easy to understand that valvular lesions may cause modifications in any or all of the organs or tissues of the body. These modifications, since they must ultimately depend upon deviations from the normal blood supply of those organs or tissues, may be either anatomical or physiological; as a rule, however, both structure and function are affected. But the remarkable fact is that in the majority of cases a valve lesion may exist for a long period, frequently for years, during which the body at large grows, is nourished, and performs its functions in a perfectly normal manner. It has been said above that in an uncomplicated case dilatation is the ultimate cause of the patient's death, and that hypertrophy is the natural cure for that dilatation. It is this hypertrophy which protects the rest of the body from the evils which otherwise would have accrued to it as the result of the valve lesion, and if the amount of hypertrophy be sufficient to fully protect the body from those evils, it may rightly be said to "fully compensate" for the valve lesion. The occurrence of complete compensatory hypertrophy, however, is dependent upon so many factors, any one of which may be inadequate, that complete compensation, in the sense that the patient is capable of living and acting as a normal healthy person, is rare. Cases have been known in which the compensation has been so complete that exertions, even so fatiguing as those of military marching during the course of a campaign, have been undergone without more than ordinary discomfort; nevertheless, it is more common to find that reserve force of the heart, though present, is not so great as it is in the normal subject; the patient, for example, can walk, but he cannot run without distress.

The amount of reserve power which is held by a heart that is the seat of compensatory hypertrophy is very variable. In one patient the reserve force may be equal to that of a normal healthy person, in another it may be sufficient to allow him to walk but not to run, in a third the patient may be able to walk on the flat but becomes breathless on attempting to mount the slightest incline, a fourth may be in comfort when driving, but cannot walk more than a few steps, while yet a fifth may experience distress at all times excepting those during which he is at rest in bed. In the last case, though equal to the maintenance of a bare circulation, the heart is unequal to the performance of even the minor exertions of life. Further, not only is the amount of reserve force that resides in a hypertrophied heart an uncertain quantity, but also such reserve force as is actually present is unstable. In the first place, for some reason that is at present uncertain, but is probably at bottom nervous, hypertrophied muscle is very liable to undergo degenerative changes; perhaps even, more prone to them than normal muscle.[1] In the second place, since the amount of reserve force available is less than normal, a greater proportion of those accidents of life which befall the normal heart—slight ailments (especially those accompanied by fever), excitement, pain, fear, etc.—and which the normal heart bears without harm, are directly injurious to the hypertrophied heart. And, in the third place, the valve lesion which is calling for compensatory hypertrophy is, in the vast majority of cases, a gradually progressive one: the fibrous tissue which surrounds a "button-hole" mitral orifice contracts yet more as time goes on; an aortic orifice, which permits regurgitation, contracts, and adds obstruction to regurgitation, or, in other cases, dilates yet more, and allows increased regurgitation. Whatever be the lesion, the ratio between it and the hypertrophy cannot remain a constant one, earlier or later hypertrophy must fail. The immediate result of that failure depends upon the valve that is affected.

Owing to the fact that the heart is provided with four valves and two muscular cavities (the auricles in this connection may be ignored), *ventricular* failure is not of necessity synonymous with *cardiac* failure. For though, to take an example, the aortic semilunar valves may be diseased in such a way as to lead to dilatation and hypertrophy of the left ventricle, events occurring in this cavity during systole are shut off from the left auricle, lungs, right side of the heart, and systemic venous system by the competency of the mitral valve. But when failure of the left ventricle sets in and dilatation gains the upper hand, the left auriculo-ventricular fibrous ring shares in the dilatation and separates the bases of the mitral flaps, and the musculi papillares carried with the ventricular wall are set further apart than normal. Under these conditions, strict closure of the mitral valve during systole is impossible, and mitral regurgitation takes place. The lungs now share in the trouble, and dyspnœa, œdema of the lungs, bronchitis may occur. The right side of the heart, however, is still protected by the pulmonary semilunar valves, though they give evidence of the stress that is upon them by accentuation of the sound they yield in their closure. But the increased tension throughout the pulmonary circulation constitutes an obstruction to the opening of the pulmonary semilunar valves, which, in the manner that has already been described in detail, leads to dilatation and hypertrophy of the right ventricle, and transmits the stress caused by the aortic lesion back to the tricuspid valve. *So long as the tricuspid valve is competent, though heart and lungs suffer, the body at large is safe.* But once dilatation of the right ventricle has gone so far as to permit tricuspid regurgitation, "cardiac failure," with its train of symptoms, sets in, and every organ and tissue of the body is called upon to bear the brunt of the aortic lesion. Now, the pressure in the systemic veins is increased, as was at an earlier period the pressure in the pulmonary veins, and the effects of chronic venous congestion show themselves; the liver becomes altered and the exercise of its functions impaired, the kidneys are anatomically changed and no longer secrete normal urine, the alimentary tract is disorganised and dyspepsia results, the skin, subcutaneous tissue and muscles become œdematous and lose their normal elasticity, fluid collects in the serous cavities and there produces its own particular pressure symptoms, the functions of the brain become disordered, and delirium, insomnia, hallucinations or other troubles result. Such is the picture of the latter end of valvular disease if it goes on to its natural termination: the tricuspid valve holds the key of the situation, but only so long as the right ventricle allows.[1]

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[1] The best examples of degenerative changes following on hypertrophy are found in cases where a certain group of muscles has become hypertrophied owing to its particular use in the patient's vocation; of this kind are "hammerman's palsy," and allied conditions.

III. **The Pathology of the Myocardium, excluding changes due to valve lesions.**—We have already described how the heart muscle may become thinned by dilatation or thickened by hypertrophy as the result of valve lesion, but disease of the valves of the heart is not the only method whereby secondary myocardial changes such as those hitherto dealt with may be brought about. They are also induced by morbid changes in other parts of the body. Most important of these are conditions which oppose obstacles to the opening of the pulmonary or aortic semilunar valves by raising the blood pressure in the pulmonary or systemic circulation. Hence it is found that changes in the right side of the heart are caused by various diseases of the lungs, changes in the left side of the heart are caused by various morbid conditions of the systemic arteries. The latter we shall not discuss here, for they fall more naturally under the pathology of the blood-vessels, but concerning the former a word may be said.

So far as the lungs are concerned any morbid condition which impedes the circulation through them leads to changes in the right ventricle. For reasons that have been given that change is most commonly in the way of dilatation. Chief among the conditions is the morbid change known as "emphysema," in which the walls of the alveoli are stretched and their elasticity is lost. Since the pulmonary capillaries run in these alveolar walls it follows that they too are stretched and, therefore, that their lumen is narrowed. Now, the viscosity of a fluid being constant, the resistance which that viscosity presents to the onward flow of the fluid through a tube, varies inversely as the square of the diameter of the tube through which the fluid is passing. Hence the work that is thrown upon the right ventricle in forcing the blood through the narrowed and elongated capillaries is enormously increased and dilatation ensues: in time this leads to tricuspid regurgitation and cardiac failure. But emphysema, though perhaps it may at times be a primary disease, nevertheless is in the vast majority of cases secondary to either chronic bronchitis or asthma; hence chronic bronchitis and asthma with emphysema may be regarded as the chief pulmonary causes of dilatation and hypertrophy of the right ventricle.

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[1] We are not concerned here with therapeutics, otherwise it might be shown how the whole aim of treatment in heart disease is directed towards averting the onset of cardiac failure and favouring hypertrophy. The two principles which guide the physician are (1) diminution of the amount of work demanded from the heart, (2) improvement of the nutritive condition of the heart muscle. Measures which do not conform to either of these two principles are valueless, if not directly harmful.

It might be expected that cardiac changes would be brought about when, *e.g.*, a new growth, or acute croupous pneumonia, or tubercular infiltration, or pleural effusion leading to compression has obliterated the larger number of pulmonary capillaries, or at all events has greatly impeded the flow of blood through them, and to some extent this is the case. But there is a marked difference between a process which affects practically all the pulmonary circulation, such as the emphysema induced by long-standing chronic bronchitis or spasmodic asthma, and a process that affects a portion only of the pulmonary vessels, though in the latter case the individual vessels may be far more seriously involved. This is well shown by an experiment made by Lichtheim twenty years ago. He found that, by ligature of branches of the pulmonary artery, the united sectional area of permeable vessels may be reduced to nearly one-fourth of its normal dimensions, and yet the increase of pressure in the pulmonary artery is but trifling (6 mm. Hg.). The blood which normally passed through the two lungs now passes through only a small portion of one of them, but dilatation of the still pervious vessels and acceleration of the blood flow suffices to prevent any serious results. It is this fact which explains the general absence of dilatation and hypertrophy of the right ventricle in such diseases as we have mentioned above. To a certain extent they must and do occur, but only when the amount of lung involved is very considerable, while it is only in the rarest instances that they lead to subsequent tricuspid regurgitation and cardiac failure.

In emphysema the lung condition is chronic, and hence there is time for the occurrence of hypertrophy of the right ventricle, but in some morbid conditions of the lungs the onset is so sudden and severe that acute dilatation of the right ventricle without hypertrophy is the result.

Such a result occurs in asphyxia, whether it be produced by direct laryngeal or tracheal obstruction or depend upon interference with entry of air to the air-sacs lower down. Apart from such causes as strangulation and impaction of foreign bodies in the glottis, the heart affection may be induced by œdema of the glottis, by diphtheria, in which the larynx is often entirely or almost entirely closed by the so-called false membrane, by acute bronchiolitis, in which the bloody exudation and thin mucus poured out in the bronchioles is churned with air by the respiratory movements into a pink tenacious foam that prevents the entrance of air into the air-sacs, in drowning or in other conditions in which liquid is inspired into the lungs, and so on.

Though cardiac failure occurs in these acute asphyxial cases as it does in chronic pulmonary and in valvular diseases, the rationale of its production is different. In asphyxia the aortic blood pressure rises considerably, but though this rise of pressure acting backwards through the lungs must assist in producing the final result, it is more probable that the true reason of acute cardiac dilatation in asphyxia is to be sought in the venosity of the blood and in the descent of nervous impulses from the bulb to the heart. For when the bulb is supplied with blood containing more than a minimal amount of carbonic dioxide, certain of the nerve centres situated in the bulb are stimulated, and amongst them the vagus centre. The heart thereby becomes slowed, and the output of both ventricles is diminished. The pressure in the systemic veins rises, and that rise is greatly aided by the excessive muscular exertions involved in the forced respiration which the asphyxia also induces; occasionally the rise of venous pressure thus produced is sufficient to lead to increased output from the right ventricle in spite of the vagus inhibition. At the same time, accelerator impulses are constantly reaching the heart and tending to produce more rapid contraction. Hence four forces are acting upon the right heart: (1) upon the ventricular wall are acting (indirectly) accelerator impulses which call for contraction of the ventricle at whatever cost, on behalf of the body generally, and besides them (2) inhibitory impulses which, though protecting the heart, nevertheless at the same time lead to diastolic dilatation of the ventricle; (3) behind is an enormously increased venous pressure; and (4) in front is an impediment in the shape of increased aortic pressure. But from the nature of the case the initial difficulty, *i.e.*, the deficient aëration of the blood, not only continues but becomes rapidly more urgent, and ultimately the cardio-inhibitory centre itself becomes asphyxiated and ceases to act, and the heart, left in a dilated condition and having itself been supplied during the crisis with venous blood, is given over to the unrestrained action of the three remaining forces. Unrestrained by vagus action, and perhaps directly urged by the accelerators, overfilled during diastole, it contracts rapidly but feebly, until at last the dilatation is such and the exhaustion of the ventricle is such that it can no longer cope with its contents. Even then the whole reserve power of the ventricle is, as a rule, not used up, for if an incision be made into the arrested right ventricle of a dog that has been asphyxiated, there will be a short return of systolic contraction when a portion of the imprisoned blood has escaped through the artificial opening.

We may conclude, therefore, that diseases of the lungs produce cardiac dilatation in two ways: (1) by way of emphysema they offer a resistance to opening of the pulmonary semilunar valves, and thereby increase the work of the right ventricle, and since this is generally more or less chronic, hypertrophy occurs along with dilatation; (2) by way of asphyxia they produce (*a*) hyper-distension of the right ventricle from reflex vagus action and from increased pressure in the systemic veins, and (*b*) impairment of muscular nutrition of the right ventricle from venosity of the blood which supplies the muscular tissue, from exhaustion that occurs when vagus action no longer restrains the rate of contraction, and probably also from endeavours to answer the incessant calls that reach the right ventricle through the accelerator nerves.

So far the conditions of the myocardium we have considered have been included under hypertrophy and dilatation with atrophy, but the heart muscle may also be affected by all other changes to which muscular tissue elsewhere is liable. It may undergo inflammation (myocarditis), indeed in all cases of pericarditis and endocarditis a greater or less amount of myocarditis is present; it may undergo degenerations, of which cloudy swelling and fatty degeneration are the most common and important, though other forms of degeneration are also known; it may be the seat of fibroid change or of various kinds of new growth or parasite; it may be called upon to work when the bodily temperature is raised. Under all of these conditions the muscular efficiency is modified and in one direction: it is rendered less capable of performing its function. An inequality between work demanded and power to do work is therefore set up under these conditions as it is set up when a valve lesion is produced. But the difference between the two cases is that whereas conservative changes in the myocardium may compensate for a valve lesion, an affection of the myocardium itself *ipso facto* deprives the heart of its last means of defence. In this lies the great danger of organic disease of the heart muscle. In many cases, particularly in those that are acute, it is not only the heart muscle which suffers, but also the other constituents of the heart wall, fibrous tissue, blood-vessels, and even nervous elements.

The natural termination of diseases of the myocardium is by way of heart failure, which is common, or by way of rupture of the ventricle, which is rare. If the condition end by heart failure all the symptoms of that condition, cardiac as well as general, show themselves even to the presence of mitral and tricuspid murmurs. The sounds of the heart, even before definite cardiac failure sets in, are "slapping" or feeble, and the heart endeavours by rapidity of action to make up for its want of force. As might be expected, a murmur if present is soft, sometimes almost inaudible, or it may not amount to more than an "impurity" of the first sound. Cardiac impulse may be imperceptible or, if perceptible, is of very short duration. In every way the heart gives evidence of inability for sustained contraction. Moreover, the very endeavour to do its work, of a heart whose muscle is diseased, is accompanied by a greater expenditure of energy than would be the case if the same amount of work were done by a healthy heart: the diseased heart works not only badly, but also wastefully, and hence mere action further aggravates the tendency to cardiac failure.

If the condition end by rupture, this usually takes place in the left ventricle as being the one exposed to the greatest stress, and at or near the apex as being the thinnest and least supported part of that ventricle; it is brought about by the attempt of the heart to meet a sudden demand which is excessive for it in its enfeebled condition. Rupture leads, of course, to rapid death, and, as has already been said, this is not, as might at first sight be imagined, from hæmorrhage, for only 150–200 c.c. of blood is effused, but from the sudden increase in intra-pericardial pressure that is brought about by the accumulation of blood. A heart in which rupture occurs is usually the seat of either fatty or fibroid change.

It is obvious that disorders of the myocardium ultimately depend upon a disturbance between the relations of the heart muscle and the blood. In the case of chronic cardiac disease, changes in the blood can only be surmised; but in anæmia, and especially in that form which is known as pernicious anæmia, both of which blood conditions lead to fatty degeneration of the myocardium, the modification of the blood is manifest.

The effects of blood-changes upon heart action has been investigated by several authors. Ringer found that without the presence of a lime salt in the circulating fluid contractility of the isolated frog's ventricle cannot be supported, that lime salts greatly delay diastolic dilatation, and that this effect of lime may be neutralised by salts of potassium. He found also that production of acid, particularly that which is formed in the course of and as the result of muscular contraction, is also inimical to cardiac contraction, but that the action of the acid may be obviated by washing the heart with a weak solution of sodium bicarbonate, which acts not by virtue of its elementary composition, but by virtue of its alkalinity. A. H. White carried the matter somewhat further, for he found that in the absence of certain salts, the most important of which are sodium carbonate, calcium chloride, and potassium chloride, the nutrient medium which is necessary for sustaining the frog's heart outside the body cannot be utilised. In any case, he finds that a heart cannot contract at the expense of its own substance.

In acute febrile diseases the heart invariably suffers; in some cases the mere rise of temperature seems to act alone, but in the majority, *e.g.*, diphtheria and septic diseases, the injurious substance is apparently a bacterial toxin which is circulating in the blood. Roger isolated from cultures of *B. septicus putidus* a toxin which, in the frog, slows the heart, increases the length of systole, and finally causes standstill in diastole like muscarin; while poisoned, the heart cannot be stopped by excitation of the vagus, nor does it react to direct faradic stimulation of the heart muscle. In diphtheria, Samschin found that the heart muscle undergoes fatty and hyaline degeneration, patches of which are localised especially in the neighbourhood of the blood-vessels; in acute cases the intima and media of the small arteries are seen to be fatty; he found no changes in the nervous elements. Scagliosi, on the other hand, while agreeing with Samschin so far as concerns the parenchymatous and the vascular changes, observed marked degenerative changes in the nerve cells in addition. In acute endocarditis generally Kusnezow found that the cardiac ganglia are in a condition of inflammatory granulation, that proliferation of the capsular endothelial cells occurs, and that the ganglion cells themselves are disorganised, being the seats of cloudy swelling and of fatty and pigmentary degenerations. Evidence is therefore not wanting that the condition of the myocardium is dependent upon the composition of the blood.

But the nutrition of the heart muscle not only suffers from modifications in the quality of the blood which it receives, it may also be affected by modifications in the quantity. In this connection must be considered pathological changes of the coronary arteries and angina pectoris.

*Angina Pectoris.*—It is an accepted fact that angina pectoris is very frequently associated with atheromatous degeneration of the coronary arteries or of the aorta immediately about the orifices of these arteries. Now such a condition is an obstruction to the supply of a due amount of blood to the myocardium, and since, in cases of angina pectoris, the heart after death is found fatty, flabby, dilated and in diastole, there is reason to believe that the disease depends upon a mal-nutrition, such as the atheromatous condition of the arteries could produce. Angina pectoris is a disease, which, in addition to causing paroxysms of extreme agony in the præcordial regions, is not infrequently a cause of sudden death. The following case related by Œstreich is very instructive. An officer, aged 32, apparently in perfect health, died suddenly after coitus, and at the autopsy the following condition was found. The heart was as large as the clenched fist, flabby, and both ventricles were filled with fluid blood and in diastole. The heart muscle was greyish-red, friable, and microscopically showed fragmentation.[1] Immediately above the right aortic valve a thrombus, with a thin pedicle and about the size of a cherry-stone, projected from the wall of the aorta. The pedicle and that portion of the thrombus which lay upwards and towards the right consisted of yellowish-grey and dryish substance; below and towards the left it was dark red and more liquid. The thrombus was slightly movable upon its pedicle, pendulous, and on opening the heart was found in such a position as to completely cover the orifice of the right coronary artery. This artery in its course was partially filled with fluid blood, the walls were soft, in a few places were yellowish spots, but no calcification was present. At the commencement of the left coronary artery was a yellowish-grey embolus about 1 cm. in length, the composition of which was the same as that of the upper portion of the thrombus already described. The left coronary artery presented the same appearances as the right. Immediately above the left aortic valve the intima of the aorta was yellowish, thickened, and showed several quite small atheromatous ulcers; the remainder of the aorta was healthy except for localised patches of fatty change in the intima. The other organs were healthy. In correspondence with the clinical data the pathological evidence gave the following explanation of the case. There was a commencing atheroma of the aorta in an apparently healthy man. A polypoid thrombus had formed on one of the very small atheromatous ulcers, and this obliterated the right coronary artery: a portion broken off from this thrombus during exertion obliterated the left coronary artery. Death was rapid but not instantaneous. In this case the lesion was slight but sufficient; in others, amongst which the classical case of John Hunter may be mentioned, the whole of the coronary arteries may be converted into rigid calcareous tubes.

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[1] The pathological significance of fragmentation is at present uncertain; the subject will be considered further in chapter xv.

Now it is comparatively easy to test the effect of sudden obstruction of a coronary artery upon the heart's action by ligaturing one or more of the branches of those arteries in the lower animals. This experiment has been performed many times since v. Bezold found that on compressing the left coronary artery in the rabbit the heart of the animal quickly ceases to beat. In the dog, Cohnheim and Schulthess-Rechberg observed that ligature of any large branch of either right or left coronary artery "has at first no effect whatever upon the rhythm or vigour of cardiac contraction nor consequently upon the blood-pressure but after the lapse of ninety seconds on an average the heart beats begin to be somewhat irregular and infrequent, yet still without affecting the blood-pressure, till suddenly and at the same instant both chambers stop in diastole. From this standstill, which occurs on an average not later than two minutes after occlusion of the branch artery, there are no means of arousing the ventricles to new life and renewed contraction; it seems as if a deadly poison had for ever destroyed the heart's excitability. Accordingly it is in all probability the system of ganglia which is affected in this direct fashion. . . . Yet I am unable to conceive how with a marked independence of the muscles of the left and right ventricles[1] the one from the other (of which I shall produce numerous proofs further on), a limited arterial ischæmia could in such deadly manner paralyse irrestorably the whole cardiac musculature. For I repeat, the closure of one or both coronary arteries is not necessary; any one branch of a certain size, no matter which, is sufficient."[1]

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[1] See below, pp. 90 and 91.

Though certain minor differences obtain between the results of different investigators, and though v. Frey maintains that stoppage of the heart is not a necessary result of closure of a large branch of the coronary arteries and that similar results may be brought about by numerous other interferences with the heart, so that stoppage of the heart, when it occurs in the experiment under discussion, is probably also dependent upon secondary injuries, yet Michaelis (1894) and Townsend Porter (1894), on a careful repetition of Cohnheim and Rechberg's work, fully corroborate their statements.

Comparing Œstreich's case with the results of experimental obstruction the correspondence is seen to be almost complete, though a difference exists in the fact that pathological evidence in the former case seems to point to the possibility of the existence of complete obstruction of the right coronary artery for some time without fatal results. Whether the thrombus over the right artery, however, which evidently from its composition had existed for perhaps days, caused complete obstruction, it is difficult to say; it seems more probable that a certain though diminished volume of blood reached the myocardium by this vessel, and that, though the obstruction was not sufficient to cause sudden death as in experimental obstruction, it was nevertheless sufficiently severe to bring about the myocardial degeneration which was found at the autopsy. In any case the general correspondence is so close that we are probably correct in looking upon angina pectoris as being dependent both so far as concerns the myocardial changes and as concerns the occurrence of sudden death upon obstruction to the flow of blood through the coronary arteries. An explanation of the most prominent symptom and the one from which the disease derives its name, *i.e.*, the torturing præcordial pain, is more difficult, but if we bear in mind that the heart during a paroxysm is dilated and distended with blood, that according to Smirnow there is immediately beneath the endocardium a rich network of afferent nerves, and that rapid hyper-distension of muscular organs with fluid contents is known in other cases (*e.g.*, urinary bladder) to produce extreme pain, we may provisionally conclude that anginal pain is due to stretching of afferent nerve-fibrils. With regard to the ultimate cause of sudden death in angina pectoris we can go no further than the hypothesis which Cohnheim put forward to explain the ventricular arrest in his experiment.

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[1] Cohnheim's *Lectures on General Pathology*, English translation, vol. i. p. 35.

IV. **The Pathology of Congenital Malformation of the Heart.**—Owing to the fact that experimental teratology is yet in its infancy we are at present completely ignorant of the causes which lead to imperfect development of the heart, but the clinical symptoms produced in congenital heart malformation are in so many respects dissimilar from those of acquired heart disease (whether primarily valvular or primarily myocardial), that it has been thought advisable to deal with them briefly in a separate section.

Congenital malformations may be divided into two great classes according as they are or are not compatible with extra-uterine life. The latter are of embryological interest, but do not concern us here. Amongst the former are found conditions varying in degree of development from that described by Wilson where the auricle and ventricle were undivided, and there was a single artery which gave off a vessel sending branches to the lungs and branches to the head and upper extremities, and where the child lived for seven days, to conditions in which an amount of stenosis obtains at the orifice of the pulmonary artery that is so slight as in nowise to interfere with the comfort or longevity of the patient. But the persons who are regarded as being the subjects of congenital heart disease, and who, many of them, live to early adult life, present lesions which lie between these two extremes. It may be that the foramen ovale is not closed, that the inter-ventricular septum is in part deficient, that the ductus arteriosus is patent, that some of the valves of the heart are abnormal (and during life it is impossible to decide which of these conditions is present), but in any case the pathological effects of the condition are practically identical throughout. For congenital heart disease invariably signifies (*a*) sluggish circulation, and (*b*) deficient aëration of blood.

The venosity of the blood gives rise to a cyanosis which is pronounced according as the malformation is considerable; in some cases there is but a bluish tinge of the extremities, in others the whole countenance is livid. Owing to the venous congestion, the fingers and toes become "clubbed" and the nails curved, appearances that are very characteristic of this form of heart lesion. The sluggishness of the circulation combined with the venosity of blood which it exaggerates, accounts for the chilblains, ulcerations, etc., that occur. Dyspnœa on exertion is easily explained by the natural venosity of the blood, and the lack of power on the part of the heart to force the blood more rapidly through the lungs. For the same reason, bronchitis and other similar pulmonary affections are common. The most notable difference from other forms of heart disease is, that in congenital heart disease dropsy is extremely rare;[1] but in other respects it is clear that the symptoms differ only in degree from those of acquired heart disease. Cyanosis, the results of venous congestion, hypothermia are more marked, and the effects of intercurrent disorders, particularly those of the lungs, are more severe, but fundamentally the pathology of the two classes of lesion, as might be expected, is identical.

V. **Pathological Variations of Cardiac Rhythm.**—Under ordinary circumstances the heart contracts about seventy times per minute, and the contractions—except for such modifications as are introduced by normal respiration—are equal in duration, and follow one another at equal intervals of time. Still within the confines of physiological action the rapidity of heart beat may increase up to 100 per minute or more, as the result of mental excitement or muscular exertion, or may diminish to perhaps 50 per minute during repose, and especially during sleep. But apart from these physiological variations, cardiac action may be altered more or less profoundly in a sense that may fairly be denominated pathological. Of pathological variations in cardiac rhythm we may distinguish two kinds:

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[1] To this point we shall return when discussing the pathology of exudation.

firstly, those in which the variation is associated with some recognisable lesion of the heart or of some other part, and secondly, those in which the modification of rhythm is, so far as can be at present recognised, the substantive disease. This latter class comprises the so-called "functional" diseases of the heart, a term useful enough so long as it does not blind us to the fact that the cause of the variation in cardiac action is only unknown, not non-existent nor even unknowable.

Cardiac rhythm may be modified in four ways: 1, the rate of beat may vary; 2, the strength of beat may vary; 3, the length of diastole may vary; 4, the normal synchronous action of the two ventricles may (perhaps) give way to asynchronism. In many cases two or more of these variations may co-exist; thus, in ordinary febrile states not only is the heart's action more rapid than normal, but also the strength of the individual beat is diminished, and diastole is shortened. Such a condition differs from a physiological increase of rapidity in the fact that in fever the strength of individual beats, as represented by the duration of systolic contraction, is diminished, whereas physiological increase of rapidity is almost, if not entirely, dependent upon a diminution in the length of diastolic pause.

*Tachycardia.*—Increase in rate of cardiac rhythm is relatively simple, and occurs under the name of *palpitation* or *tachycardia* in a variety of diseases, the greater number of which are functional. The palpitation of dyspepsia (to take a specific example) we may probably regard as being brought about in the following way. It is known that afferent impulses brought to bear upon a nerve centre which is in the act of discharging efferent impulses, inhibit the action of that centre. In dyspepsia, afferent impulses passing from the stomach by the gastric branches of the vagus up to the centre in the medulla oblongata, find the cardio-inhibitory portion of that centre in the act of discharging tonic efferent impulses to the heart; the discharge of these efferent impulses is therefore inhibited, and the result on the heart's action is the same as when inhibition is brought about in the normal manner and heart action is quickened by impulses passing along the accelerator nerves. Most of the varieties of tachycardia probably in the same way depend upon inhibition of the tonic action of the cardio-inhibitory centre, though the nerves whereby the afferent impulses are conveyed to the medulla must be very numerous and different, judging from the analogy of physiological increase in rapidity of heart beat. So far as the tachycardia that constitutes a chief symptom of exophthalmic goître or Graves's disease is concerned, its pathology is quite unknown; though the subject will be left for later treatment it may be mentioned here that one view is that degenerative changes in the cervical sympathetic ganglia act as stimuli to the accelerator nerves. In yet two other conditions tachycardia is occasionally a prominent symptom, viz., as a sequel to influenza and to diphtheria. It is possible that here we may have a clue to the explanation of many forms of tachycardia, and that they may be found to depend upon some toxic action upon nerve centres; poisons (*e.g.*, aconite) are already known which produce acceleration of the heart.

*Bradycardia*, in which the rate of heart's beat is diminished and in which length of diastole and strength of beat are increased, is a much rarer variation of rhythm than tachycardia; in some individuals bradycardia is normal. Like tachycardia it may be due to the action of poisons (*e.g.*, digitalis). Bile-salts also produce bradycardia, and their circulation in the blood explains why in certain forms of jaundice the pulse-rate is reduced to 50, 40, or even 20 per minute. Some other forms of bradycardia, as we shall see, are really cases of alternating heart beat.

*Intermittence* is a pathological condition of cardiac rhythm of but little clinical significance if it alone be present; in many cases the intermittence of a beat every now and then might almost be regarded as normal, while an extra cigar or glass of port wine is frequently sufficient to bring it about. Sometimes the intermittence is regular, *i.e.*, the number of regular beats between two dropped beats is the same, sometimes it is irregular. As a rule, the beat which follows a dropped beat is stronger than its fellows, and in this way compensation is made for the intermission. The reason of this, no doubt, is that the ventricle after an intermission is fuller of blood than usual, and a portion of the reserve force of the heart is called upon to empty it. Concerning the cause of intermittence itself no satisfactory explanation can be given.[1]

In some cases ventricular systole is alternately strong and weak, the diastolic pause between any pair of beats being, however, always the same; or a weak systole may follow rapidly on a strong beat and before the next strong systole a long diastole may intervene. It is evident that if such a heart be contracting at the rate of 70 per minute, and the weak beats be so far weakened as to become imperceptible to ear or touch, the recognisable rate of heart beat will be 35 per minute, and apparently bradycardia will exist. This is not really the case, however, as the weakened beats may be rendered recognisable by causing the patient to undergo slight muscular exertion, when 70 contractions per minute will again be present or perhaps 80 or more, and the alternating character of the rhythm will show itself. In true bradycardia with an initial rate of 35 beats per minute, such exertion would only lead to a rate of perhaps 45 beats per minute, and alternation would be completely absent.

*Irregularity.*—So far we have been considering variations of rhythm in which regularity is dominant; there is another class of case in which the heart's action is completely irregular; beats follow one another at irregular intervals and are of irregular strength, intermittence occurs, but it too is irregular. This form of variation is of much greater importance than those we have hitherto discussed, and is frequently, if not invariably, associated with some organic disease of the heart itself. The cause of the condition is uncertain, though it must assuredly be dependent upon perverted nerve action, whether of the intrinsic or of the extrinsic nervous elements of the heart or of both it is hard to say; but it seems probable that the intrinsic nerve elements must play an important part in view of the changes that have been observed in the cardiac ganglia in endocarditis.

Roy and Adami suggest that one cause of irregularity is the interposition of idio-ventricular beats such as those which are seen when the heart is exposed to powerful vagus action. Since irregularity of cardiac rhythm becomes most evident when the heart begins to fail, a time at which increased demands are being made on the heart, and therefore at which it is more than probable that vagus action is increased in order to protect the heart, this suggestion most likely contains some truth. François-Franck considers that the irregularity of the heart in mitral insufficiency (and this may stand as a type for all kinds of irregularity in cardiac rhythm) depends upon myocarditis or endocarditis; he found that he could produce irregularity at will by irritating the endocardium with a cardiac sound. Moreover, Rodet and Nicolas observed irregularity of heart action, transient it is true, as the result of traumatic stimuli (incisions, pricks) of the myocardium. Nevertheless, irregularity is probably at bottom nervous and not muscular in origin, and hence the opinions given above practically amount to the single view that the discharge of energy from the cardiac ganglia becomes irregular under the influence of an irritant of some description acting either locally or from a distance. Unfortunately, such an explanation is not of great assistance, indeed it almost amounts to a confession of complete ignorance upon the point.

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[1] See below, p. 90.

With regard to intermittence generally, and in mitral insufficiency in particular, much discussion has taken place as to whether hemisystole or the contraction of one ventricle without the other can take place. Leyden held that such a condition can obtain, and explained the intermittence as being due to failure of a left ventricular contraction, the right contracting as shown by pulsation in the jugular vein. Recently (1894) Arloing stated that, with prolonged stimulation of the right vagus in the horse, on one occasion he found the right ventricle beat more slowly than the left, *i.e.*, that hemisystole was present. But François-Franck, by means of cardiac tracings taken from man and the dog (the latter intra-cardial), has proved conclusively that the two ventricles contract simultaneously, and that aborted systoles in one appear in the other also. On the whole, therefore, it must be concluded that though hemisystole is possible, it is so extremely rare that it may be left out of consideration. This is contrary to the teachings of Cohnheim and of Leyden.

It has been held that the double sound which is at times heard at the apex of the heart is due to asynchronism of first sounds formed in the right and in the left ventricle, but it is probable that the so-called reduplicated first sound is indicative of some valvular—probably mitral—incompetence and is of the nature of a murmur, especially as other signs of mitral incompetence are usually present when such reduplication of the first sound is heard. There is no doubt, however, that reduplication of the second sound occurs, for not only is it distinctly audible, but also it is clearly possible that the pulmonary or the aortic tension may become so increased, that closure of the semilunar valves on that side on which the tension is increased takes place earlier after all the blood ejected in systole has left the ventricle, than it does on that side on which the tension is normal or perhaps even diminished. This is probably the only form in which asynchronism occurs, at all events in higher animals. That the ventricles are essentially independent we know from physiology, but whether they ever act independently, except when artificially separated, is another and a much more doubtful question.

*Note.*—The following summary account of the nervous regulation of the heart may be of use:—The heart is controlled by nerve fibres which travel from the bulb in the trunk of the vagus, and by nerve fibres which reach the heart from the dorsal-spinal cord, having passed through the sympathetic chain. Those fibres which reach the heart by the vagus are connected centrally with the cardio-inhibitory centre, are tonic and inhibitory in action, and influence the heart through the cardiac ganglia. Those nerves which, coming off from the dorsal-spinal cord are connected with cells in the stellate ganglion, from the results of their action are known as augmentor or accelerator nerves; they do not act directly upon the heart, but indirectly by inhibition of the vagus, and, so far as is known, are not connected with the cardiac ganglia. In addition to the above, afferent impulses, starting probably in the sub-endocardial and sub-pericardial regions, are able to leave the heart; the path whereby they travel is, in the main, the depressor nerve of the rabbit or its representative in other mammals, and it is possible that afferent impulses may also travel up by way of the vagus; in either case these afferent impulses are conveyed up to the vaso-motor centre, and through it influence particularly the vessels in the splanchnic area. Besides the nerves mentioned, the heart possesses in some degree the power of automatic action. So far as function is concerned it may be said that the vagus protects the heart at the expense of the body, the accelerator nerves waste the heart for the advantage of the body; while the cardiac ganglia, besides modifying, in all probability, the impulses they receive through the vagus, appear to have also the power of maintaining the circulation, in spite of strong vagus opposition.

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# CHAPTER IV.

## The Pathology of the Circulation (*continued*)—The Blood-Vessels.

*Synopsis.*

I. General Considerations.

II. The Effects of Pathologico-Anatomical Changes in the Blood-Vessel Wall:
  - (i) On the Elasticity of the Vessel.
  - (ii) On the Calibre of the Vessel.

III. The Effects of Diminished Elasticity of the Vessel Wall:
  - (i) On the Vascular System:
    - (*a*) When Rigidity of the Vessel is increased.
  - (i) On the Vascular System:
    - (*b*) When Rigidity of the Vessel is diminished. Aneurysm.
  - (ii) Upon the Liability of Blood-Vessels to Rupture.

IV. The Effects of Local Diminutions of Arterial Calibre (Ischæmia). Embolism. Thrombosis. Infarct. Ergotism, Pellagra, and Raynaud's Disease. Temporary Ischæmia.

V. Local Congestion.

VI. Effects of Hæmorrhage.

VII. Venous Pulsation.

VIII. Capillary Pulsation.

I. **General Considerations.**—From our point of view morbid conditions of the blood-vessels are chiefly of importance by virtue of their effects upon the circulation of the blood. The elasticity of arteries or of veins may be diminished, their calibre may be increased or diminished, they may suffer solution of continuity, and we have to consider the effects of such changes upon (*a*) the blood-vessel at the seat of change, (*b*) other blood-vessels, (*c*) the heart, (*d*) the tissues. The means whereby the vascular changes may be induced are numerous; thus diminution in calibre of an artery may depend upon anatomical or upon nervous causes, upon obstruction from within, or upon pressure from without, while many of these causes might be further subdivided. The same is true for the other changes. Moreover, one and the same process does not always lead to the same result; this will clearly be recognised when considering the effects of embolism or of atheroma.

II. **The effects of Pathologico-Anatomical Changes in the Blood-vessel Wall.—(i.) On the Elasticity of the vessel.**—Since atheroma is the commonest pathological change undergone by arteries, being absent in but few persons above the age of thirty years, changes in elasticity of arteries may very naturally be associated with atheroma. But a moment's reflection affords reasons for believing that atheroma and loss of elasticity of the arterial wall stand to one another in the relation of cause and effect. When we consider that in atheroma of the aorta the vessel wall may be replaced over areas varying in diameter from one to twenty millimetres or more by a fatty and granular detritus, which is at times held in position by little more than a layer of endothelium covering it, and which often involves as much as one-half of the thickness of the aortic wall; or that in other cases, owing to the deposition of lime salts in the atheromatous and fatty material, the inner coat of the aorta has come to consist of a more or less continuous calcareous plate (arteritis deformans), we cannot fail to conclude that atheroma must be the commonest cause of diminished elasticity of the aorta.

The last work of importance that has appeared in this country upon the elastic properties of the vessel wall is that by Roy in 1880. He pointed out that animal tissues differ from most other substances in thermo-elastic properties; they contract on being warmed, and expand on being cooled, on being stretched their temperature rises and falls again when they are relaxed. He showed that arteries are most elastic and most distensible with internal pressures at or near those which obtain in them during life, for, in the case of the aorta and large arteries with which he chiefly worked, he found experimentally that the maximum increase in capacity is reached with unit increase of internal pressure, when the internal pressure is at or about the mean blood-pressure of the animal from which the specimen was taken. In adult man he found the elasticity of the vessels less than in the lower animals, and showed that in man with advancing years the elasticity of the aorta to the higher pressures diminishes markedly. The elasticity of arteries is readily modified by diseases affecting the general nutrition; slow febrile and wasting diseases may completely modify the curve of elasticity, so that the arteries are found after death from such diseases relatively wider than normal, and most distensible with pressures immediately above zero, in this latter respect conforming to what is normal for the elasticity of veins. It is hardly necessary to point out that hyper-distension long kept up and inflammatory processes, by altering the constitution of the vessel walls, impair their elasticity, nor that, owing to the superiority of arterial over venous blood-pressure, loss of elasticity is of greater importance in the arteries than in the veins.

(ii.) **On the Calibre of the Blood-vessels.**—The changes may be in the direction of (A) diminution, or (B) increase, and may be either general or local.

A. **Diminution in Calibre.**—In the case of arteries the chief causes of diminished calibre are atheroma, arterio-sclerosis, endarteritis obliterans. In the aorta, atheroma rarely leads to narrowing or stenosis, unless it involve the aortic semilunar valves, but if the degenerative process be very widely distributed in the body, smaller arteries, such as the radial, may become affected. In such cases the condition is almost invariably accompanied by a deposition of calcium salts in the atheromatous patches, and the walls of the arteries may become converted into rigid calcareous tubes. Not only in these cases is the elasticity of the affected vessels abolished, but also the calcareous deposit encroaches upon the lumen of the tube to such an extent that at times it becomes well-nigh impervious. A similar narrowing of the lumen of the smaller arteries occurs in arterio-sclerosis, but though great it is not commonly so excessive as that which is found in atheroma. In this condition, too, the arterial wall, though thickened and fibrotic, has not entirely lost its elasticity, and the effects produced upon other parts of the circulatory system are correspondingly different. An artery which is the seat of arterio-sclerosis may later become affected by atheroma. Both atheroma and arterio-sclerosis are more or less general processes affecting large portions of the arterial system, and the diminution in calibre to which they lead differs in character and in effects from that which is due to external pressure exerted by a ligature or a tumour, and in which the diminution in calibre of the vessel is purely local.

Diminution in calibre of veins is not important in itself, but becomes so in view of the fact that, if extensive, it may cause dilatation of the veins and congestion of the capillaries behind it, by opposing an obstacle to the onflow of the blood. It is generally dependent upon thrombosis or upon the pressure of a tumour.

B. **Increase in Calibre.**—In the case of arteries this frequently goes hand in hand with an impairment of elasticity induced by one or other of the causes that have been mentioned. When the elasticity of a vessel has become impaired, this impairment may be general or local, and, therefore, any dilatation of a vessel due to loss of elasticity may be either general or local also. Since atheroma is one of the chief causes of diminution in elasticity, it is also the great cause of local and general dilatations of arteries (aneurysm).

The small arteries may become dilated owing to the removal of the tonic vaso-constricting impulses which they receive from the medulla oblongata; this may take place in the ordinary physiological manner, or may be due to some pathological lesion, of whatever kind, affecting spinal cord or nerves in those portions of their tracts which normally conduct vaso-motor impulses. This variety of dilatation will be considered along with congestion.

In the veins, dilatation occurs principally as the result of obstruction to the flow of blood towards the heart. If the obstruction be great, the veins are kept in a chronic condition of hyper-distension, owing to the increase of venous blood-pressure within them, and gradually losing their elasticity, they become more and more dilated as time goes on. Here again the condition may be localised, as in the case of a varicose saphena vein, or may be general, as in cases where the obstruction depends upon some central lesion such as valvular disease of the heart.

**III. The effects of Diminished Elasticity of the Vessel Walls.—(i.) Upon the Vascular System.**—Since diminution in elasticity of the vessel wall is of its greatest importance in the arteries, we shall refer almost entirely to those vessels in the following paragraphs. Now the effects of such diminution in elasticity differ widely according to whether the rigidity of the vessel is at the same time (*a*) increased, or (*b*) diminished. That the rigidity may be altered in either of these two directions is easily seen in the case of atheroma of the aorta. Where the atheromatous change alone has occurred with the formation of an atheromatous ulcer, the rigidity of the aortic wall is diminished, because a portion of the thickness of the wall has been destroyed; on the other hand, where the atheromatous change has been accompanied by calcification, the rigidity of the aortic wall is increased, because a plate of calcareous material is more rigid than the elastic tissue which it replaces.

(*a*) *Rigidity is increased.*—When the rigidity of an arterial wall is increased it opposes a greater resistance to distension by the systolic increase of the blood-pressure than before, and the increase of resistance may either be sufficiently small for distension to be brought about by an increased force of contraction on the part of the left ventricle, or it may be so great that even the most forcible systole of the left ventricle is totally unable to produce any distension at all. As an example of the former class of case we have the fibrotic condition of arterioles described by Gull and Sutton, and known as arterio-sclerosis. As examples of the latter class are those cases in which extensive calcification of arteries occurs, whether that calcification be mainly confined to the aorta or involve vessels down to and including those of no greater diameter than the radial.

Now the effects that are produced upon the heart are widely dissimilar. It is a fundamental law of pathology and physiology, that if a healthy muscle is intermittently called upon to contract against an increased resistance *which it can overcome*, it hypertrophies, and thus in arterio-sclerosis the left ventricle hypertrophies. Moreover, since it is one of the inherent properties of fibrous tissue to contract, the lumina of the arterioles become more and more narrowed and lead to more and more hypertrophy of the left ventricle. So far as the blood-pressure is concerned, since peripheral resistance is increased, and the output of the heart is increased, the blood-pressure rises. It is unnecessary to go further into the pathology of the heart changes in arteriosclerosis, since they are in every essential the same as those which we have fully discussed when dealing with aortic stenosis; the only difference is that in the one case the increased resistance is interposed at the proximal end of the arterial system, in the other it is interposed at the distal end.

When calcification of the arteries occurs the heart is affected very differently. If the calcareous change be confined to the aorta, though it interposes a resistance to the emptying of the left ventricle because the aorta fails to expand during ventricular systole, and, therefore, one would imagine, should lead to hypertrophy of the ventricle, this change does not take place. The reason of this lies in the fact that the resistance to opening of the aortic valves is a compound of two factors, elasticity of the aorta and the peripheral resistance in the small arteries. If compensatory changes can take place in the peripheral resistance, the effect of rigidity of the aortic wall (so far as it does not lead to stenosis of the aorta) is minimised, and the only effect on the circulation is that the blood-current and the pulse-wave pass with a greater velocity through the rigid portion of the system, and first distend the arteries at a more distal point than usual. The heart, therefore, in these cases is not hypertrophied, indeed since atheromatous and calcareous changes are essentially associated with old age, the nutrition of the musculature of the heart is impaired, and such an aorta is found associated with a flabby and somewhat dilated heart. For reasons that are obvious the blood-pressure is lower than normal. If the calcareous change, besides affecting the aorta, affects many of the smaller arteries of the body, it interposes a resistance to the ventricular systole which, unlike that produced by arterio-sclerosis, *cannot be overcome* by increased force of heart's beat. Hence in this case also, the left ventricle does not hypertrophy, but on the other hand dilates considerably, and its walls become thinner than normal.

In all cases in which elasticity of the arteries is diminished and rigidity is increased, the vessels become elongated and tortuous, while of course they also become firmer to the touch. So far as the pulse-wave is concerned, if the artery is completely calcareous no pulse-wave can be felt at all; if, on the other hand, the vessel wall is fibrotic, the pulse-wave, partly owing to the rigidity of the walls, and partly owing to the small stream of blood which flows through the narrowed vessels, though perceptible, is not able to raise the arterial wall to so great an extent as normal. Rigidity of the wall itself, too, renders the compression of the artery by the finger and the obliteration of the pulse-wave more difficult. Hence, clinically, the pulse in cases of arterio-sclerosis is described as small, hard, and tense, while in cases of atheroma with calcification, the pulse, if present, is weak, and in advanced cases may be imperceptible.

(*b*) *Rigidity is diminished. Aneurysm.*—When the rigidity of the vessel wall is diminished as well as its elasticity, the distensibility of the wall is increased. Here, again, the most important effects are seen in the case of the arteries. The increase in distensibility of the artery may be general or local. In either case, if the dilatation exceeds a certain very small amount, an aneurysm results. The mode of formation of a fusiform aneurysm, which is after all but a general dilatation of some vessel, usually the aorta, over a certain portion of its length, is simple. When the ventricular systole adds to the transverse force exerted upon the vessel wall by the mean blood-pressure, the wall expands equally in all directions (external support being left out of the question). If the wall is healthy, the elasticity is sufficient to bring it back into the normal position before the next systolic distension takes place; but if the elasticity and the rigidity of the vessel wall are diminished, not only does the same transverse force produce a greater yielding and thinning of the wall, but also the elasticity is insufficient to bring the wall back again into the normal position before the next systolic distension occurs. Hence a slight but increasing balance is left on the side of distension, and gradually the fusiform aneurysm is formed. Though thinned, the three coats of an artery are usually present in such an aneurysm. Where the dilatation of the vessel is localised to a more or less circumscribed spot, a saccular aneurysm results. The mode of formation of a saccular aneurysm is essentially the same as that of a fusiform aneurysm, but the loss of elasticity and rigidity which precedes the formation of a saccular aneurysm is, in the majority of cases, due to the actual destruction of a portion of the vessel wall by atheroma, and the formation of an atheromatous ulcer.

If we omit the question of rupture, an aneurysm, though it is of extreme importance in other ways, is unimportant so far as the circulation is concerned. For the only effect of the dilatation is to increase the capacity of the arterial system by an amount equal to the cubic content of the aneurysm, and thereby proportionately to diminish the peripheral resistance; to some extent, therefore, it must relieve the left ventricle of work, and hence a pure uncomplicated aneurysm is not associated with cardiac change. But since so few aneurysms—at all events of the aorta—are uncomplicated, and so many are associated with atheromatous changes about the aortic valves, which lead in particular to aortic regurgitation, it is generally found that aortic aneurysm is associated with the dilatation and hypertrophy of the left ventricle which that aortic regurgitation induces.

Peripherally, however, certain circulatory changes frequently show themselves. Thus, if an aneurysm involves the innominate artery, not only will marked pulsation occur over the seat of the aneurysm, but also the pulse at the right wrist may be noticed to be smaller and to occur later than the pulse at the corresponding point on the left side.

The reason of these phenomena is as follows. The amplitude of a pulse-wave varies directly as the diameter of the vessel through which it is passing. In the aneurysm itself the diameter is great and the vessel is fairly superficial, hence the amplitude of the pulse-wave is great also and the wave itself is easily felt, or even seen. But of the amount of blood which enters the innominate artery, the major portion is required to fill the aneurysm, and the amount of blood which reaches the subclavian artery for distribution to the arm is less than normal. Now, since the diameter of an artery accommodates itself to the amount of blood which the vessel contains, and the right radial artery contains less blood than the left, the diameter of the right radial artery is less than that of the left radial artery. The amplitude, therefore, of the pulse-wave at any given point in the right radial artery is less than the amplitude at the corresponding point of the left radial artery, and the "pulse" at the right wrist is smaller than it is at the left; sometimes the diameter of the right radial artery may be diminished to so great an extent, owing to the magnitude of the aneurysm, that no pulse-wave at all is perceptible at the right wrist. The right pulse is retarded in cases of innominate aneurysm, because the velocity of the pulse-wave varies inversely as the diameter of the vessel through which the wave is passing. Since the right subclavian, axillary, brachial, and radial arteries have smaller diameters than those vessels on the left side, the pulse-wave in these vessels must actually travel with greater velocity on the right side than it does on the left, and if the wave passed corresponding points in the two axillary arteries at the same moment, the pulse at the right wrist would precede the pulse at the left wrist. That this is not the case depends upon the fact that the pulse-waves do not pass corresponding points in the two axillary arteries at the same moment. The diameter of the aneurysmal innominate artery being considerably greater than the diameter of the healthy left subclavian artery, the pulse-wave travels more slowly through the aneurysm than it does through a corresponding length of the left subclavian artery. Hence the pulse-wave reaches a given point in the right axillary artery later than it does the corresponding point in the left axillary artery, and this lateness shows itself at the right wrist, though a portion of the delay is made up by the greater speed with which the wave travels down the narrower vessels of the right arm. The same reasoning applies in the case of an aneurysm seated on any artery, and hence the arterial pulse on the distal side of an aneurysm is small and retarded.

(ii.) **Upon Liability of Blood-vessels to Rupture.**— Whether the rigidity of the vessel be increased or diminished, whether dilatation occur or no, diminution of elasticity is accompanied by an increased tendency towards rupture. Let us first of all suppose that rigidity is increased. Now in a cylinder the tearing stress exerted by a given force diminishes as one proceeds along a radius from the centre. Hence, if the force of the ventricular systole be constant, the tearing stress exerted by the blood-pressure at the moment of systole upon the wall of the vessel is greater when the radius of the vessel remains unchanged, *i.e.*, when the vessel is rigid as in calcification, than it is when the radius is increased, *i.e.*, when the vessel is distensible as in health, and, therefore, the liability to rupture in the former case is greater than it is in the latter. This statement holds, irrespective of any alteration in the vessel wall, excepting the radius. But when it is added that in those cases where rigidity occurs, the constitution of the vessel wall has been altered by impairment of its nutrition, it is clear that not only is the tearing stress exerted by the blood-pressure greater than normal, but also the power of the rigid vessel wall to resist that tearing stress is less than normal.

Where rigidity of the vessel wall is diminished and dilatation occurs, the increased tendency towards rupture must be explained in a slightly different manner. If we take a saccular aneurysm as an example, since the line drawn from the axis of the vessel to the furthest point on the wall of the aneurysm is greater than the radius of the vessel itself, it follows that the tearing stress exerted by the blood-pressure on the wall of the aneurysm must be less than it is on the wall of the vessel from which the aneurysm is formed. Now, though it is certainly true that a saccular aneurysm would be less likely to rupture than the vessel on which it is seated, *if the wall of the aneurysm were similar in every respect to the wall of the vessel itself*, this condition does not actually obtain. The wall of a saccular aneurysm, on the contrary, as can be readily seen from its mode of formation, consists of little more than the expanded adventitia, and hence is thinner than the arterial wall; moreover, in addition to the thinning which results from the distending force of the blood-pressure acting from within, the aneurysmal sac is in contact with more or less rigid substances (*e.g.*, costal cartilages or bronchus in the case of aneurysm of the ascending or transverse part of the arch of the aorta), which, acting from without, lead to pressure atrophy of the wall of the sac. Even though the wall of the sac may be no thicker than a sheet of note-paper, the tearing stress is not commonly sufficient to lead to rupture until the pressure atrophy has gone so far as to produce an actual perforation of the sac wall. A large, saccular aortic aneurysm may communicate directly with the bronchus by a pin-hole opening, and leakage of blood into the bronchus may occur for days or even weeks before some sudden exertion on the part of the patient, accompanied by more forcible action of the left ventricle, causes rupture of the sac and fatal hæmorrhage.

In both classes of case, therefore, the increased tendency to rupture which accompanies diminution in elasticity depends upon a failure of correspondence between the tearing stress exerted by the blood-pressure and the power which resides in the modified vessel wall to resist that stress. In calcification of the aorta the rigid vessel gives way, primarily because the tearing stress to which it is exposed is greater than that which the healthy vessel is called upon to withstand. In a saccular aneurysm the tearing stress exerted by the blood-pressure is actually lower than in the vessel upon which the aneurysm is seated, and diminishes with enlargement of the sac; but the wall gives way because, thinned by pressure from within and without, its power of resisting the tearing stress is diminished to a proportionately greater extent.[1]

The "dissecting" variety of aneurysm is especially associated with rupture, and differs in appearance so markedly from the varieties already described that it must be mentioned separately. In this variety, which almost always occurs in the aorta, atheroma causes a lesion of the intima, but the blood-pressure, instead of dilating the adventitia and forming a saccular aneurysm, or rupturing the adventitia and leading to fatal hæmorrhage, causes a separation of the layers constituting the middle coat of the artery. The blood, tearing up the middle coat perhaps from the junction of the ascending and transverse portions of the arch down to the bifurcation or even further, lies, therefore, between the adventitia and the intima. That it takes this course, instead of distending or rupturing the adventitia or returning through a fresh perforation of the intima into the lumen of the vessel, because it is the direction of least resistance, there can be no doubt, but to anyone who has attempted artificially to tear up the middle coat of the healthy aorta in the same manner, the force exerted by the blood-pressure seems to be utterly inadequate. This portion of the pathology of dissecting aneurysm is a complete mystery, but the experiment mentioned seems to point to the probability that the peculiar course taken by the blood will be found to depend upon some pathological condition affecting the media generally, whereby its resistance is greatly diminished. Ultimately the adventitia is ruptured also,[1] usually at a point opposite or nearly opposite to the original lesion in the intima, and this second and fatal hæmorrhage may occur a few hours after the dissection of the middle coat has been made or may be delayed for several months.

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[1] These considerations enable one to readily explain the fact that fatal intra-pericardial hæmorrhage in young adults is so often found to be due to rupture of a small, thin-walled aneurysm, the existence of which had not been suspected in life.

IV. **The effects of Local Diminutions of Arterial Calibre (Ischæmia).**—If the lumen of an unbranched tube through which fluid is passing from a reservoir be constricted at any part of its course, three results follow: 1, the velocity of flow in the proximal and distal portions of the tube diminishes; 2, the pressure in the proximal portion of the tube rises; and 3, the pressure in the distal portion of the tube falls. Now, in the case of an artery, theoretically the same results follow also, but frequently they are not obvious. This may be because the amount of obstruction is slight, for the results mentioned above vary directly with the degree of constriction, but in the majority of cases it depends upon the facts that the greater number of arteries are branched and that the branches of adjacent arteries anastomose. There is, however, a variety of artery, the branches of which do not form anastomoses, and in such, complete obstruction of the arterial lumen leads to complete arrest of blood-flow in the distal portion of the artery and in the capillaries which it supplies. Examples of these "terminal" or "end" arteries are to be found in the central artery of the retina, in the branches of the renal and splenic arteries after they have entered into the respective organs, the lenticulo-striate branches of the middle cerebral artery, and perhaps some others.

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[1] E. Rindfleisch relates a case in which healing of a dissecting aneurysm of the arch of the aorta took place, but this must be almost if not quite unique.

(i.) **Effects of occluding a Terminal Systemic Artery.**—When a terminal systemic artery is occluded the supply of blood to the corresponding capillary area is cut off, and such blood as was in the area at the moment of occlusion passes into the vein by reason of the contraction to undistended volume undergone by the portion of the artery beyond the occlusion. The capillary area involved is, from the nature of the case, cone-shaped, and the apex of the cone is at the seat of occlusion. From this point the subsequent course of events differs somewhat according to circumstances. Strictly speaking, such a conical mass of tissue should be completely bloodless and pale, and the condition should be one of complete local anæmia. This it occasionally is, as, for example, when a lenticulo-striate artery is occluded; and the subsequent changes undergone by the cone are bloodless also, for the mass, deprived of its nutrition, dies, and the soft necrotic material which results from the occlusion of such a terminal artery in the brain is colourless and is spoken of as "white softening." But in the majority of cases the conical mass becomes filled to a greater or less extent with blood, takes on a purplish colour and is known as a hæmorrhagic infarct.

The blood which fills[1] the cone and distends its capillaries to such an extent that the condition is rightly spoken of as "*infarction*," obviously does not arrive by the usual route, for the artery which normally supplies the part is occluded; and since no anastomotic arterial branches exist to convey blood by circuitous routes excepting the universally anastomotic capillaries, it follows that the blood in an infarct comes from the neighbouring capillaries or possibly the neighbouring veins. It arrives there because a difference obtains between the pressures of blood in the capillaries of the cone and in the neighbouring capillaries, which are supplied with blood by patent arteries, and it accumulates in the cone until the pressure there is equal to the pressure in the neighbouring capillaries. Moreover, since the blood is driven into the cone from all sides and no arterial force is present to urge it into the vein which corresponds to the occluded artery, it stagnates in the cone, gives up its oxygen to the starving tissue, and becomes intensely venous. The tissue elements of the cone, as a part of their mal-nutrition, lose their elasticity and become more distensible, so that an infarcted area is fuller of blood than was the same area under normal conditions, and projects from the surface if a section be made, or if, as is the case in infarct of the kidney or spleen, the conical mass of tissue supplied by the terminal artery has its base immediately beneath the fibrous capsule of the organ.

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[1] In the case of renal and splenic infarction, if the cone be large, the central portion may remain more or less bloodless to the end.

(ii.) **Effects of occluding an Anastomosing Artery.**—But the majority of arteries are not terminal, and the effects that are produced by occlusion of an artery which is provided with anastomotic branches are different. This difference of effect, since it depends upon the presence of anastomoses, itself varies according to the number and size of the anastomotic branches. If they be many and of large size, as, for example, those uniting the branches of the superior and inferior mesenteric arteries, the circuitous routes whereby the blood can reach any one part are so many, that occlusion of a single branch, though of large size, is absolutely without effect upon the tissues.

If the anastomotic branches be few and of small size, the vessel approaches towards the characters of a terminal artery, and the results produced by its occlusion lie somewhere between the two extremes of which we have already spoken. A good example is afforded by the femoral artery. The anastomotic branches about the knee-joint are small, and the amount of blood required for the nutrition of the leg and foot is large, hence the subsequent fate of the leg and foot, after ligature of the femoral artery in Hunter's canal, depends upon the condition in which the anastomotic branches find themselves at the time of ligature. When a rupture of the popliteal artery has led to the effusion of a large amount of blood in the popliteal space and the formation of a so-called diffuse traumatic aneurysm, the pressure exerted by the effused blood is so great, that the anastomotic branches about the knee are occluded, and the femoral artery in Hunter's canal becomes terminal so far as the leg is concerned. Ligature of the artery in that position, therefore, is certain to be followed by necrosis or gangrene of the leg, and has been abandoned as treatment for this kind of popliteal aneurysm. In the case of an ordinary saccular aneurysm of the popliteal artery, on the other hand, the same operation in Hunter's canal may be undertaken with good hopes of success, so far as maintenance of the nutrition of the leg is concerned. For though the smallness of the anastomotic branches, and the amount of pressure exerted upon them by the saccular aneurysm, are sufficient to cause the leg and foot, after ligature of the femoral artery, to become pale and cold, in the majority of cases this condition is only temporary. With establishment of collateral circulation, due to enlargement of the anastomotic branches, the leg and foot return to their normal state. In a certain number of cases, however, collateral circulation is not established with sufficient rapidity, and gangrene of the whole, or more commonly a part, of the foot or leg ensues.

The reason that the area fed by an occluded but anastomosing artery is still supplied with blood is to be found in the conditions which that occlusion brings about. It has been stated above that occlusion of a tube through which a fluid is passing from a reservoir causes a rise in pressure on the proximal side. Now Nicolls has lately re-investigated experimentally the effect of ligaturing a branch of a main vessel. By means of his measuring tubes Nicolls showed that the ligature raises the pressure on the proximal side to a greater degree the further the ligatured tube is from the reservoir, and that the increase of pressure shows itself throughout the system.[1] But not only does ligature modify the pressure in the system, it also modifies the velocity of flow, and in different directions, according as the main tube in the neighbourhood of the reservoir or the nearest branch above the obstruction is concerned. In the main tube the velocity of flow is diminished, but in the nearest branch above the obstruction it is increased.[1] This experiment indicates, therefore, that in occlusion of a branch of such an artery as the superior or inferior mesenteric, the pressure in the whole arterial system is raised, and the velocity of blood-flow in the first branch above the seat of occlusion is enormously increased, and, therefore, that this vessel is *par excellence* the one into which blood coming from above will pass. The facts that on the distal side of the occlusion the pressure is momentarily diminished, and that the branch above the obstruction communicates freely with collateral branches coming off from the occluded vessel below the obstruction, further assist the maintenance of the circulation in the part. Between the obstruction, however, and the first branch on the proximal side and the first branch on the distal side the blood is at rest though under great pressure. It is hardly necessary to remark that the increase of mean blood-pressure caused by the ligature is rapidly readjusted by vaso-motor changes, or that while it lasts it induces increased force of ventricular systole.

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[1] It is this rise of pressure which renders the operation for aneurysm, in which the artery is ligatured on the distal side of the sac, so eminently unsatisfactory.

*Summary.*—The effects, therefore, of complete obstruction of an artery upon the tissues which that artery supplies are of four kinds: 1, the collateral circulation is free and the nutrition of the tissues is unaltered; 2, the collateral circulation is poor and the nutrition of the tissues suffers; if a sufficient collateral circulation becomes established, the nutrition returns to normal, but if, on the other hand, a sufficient collateral circulation does not become established, the tissues finally undergo gangrene or necrosis; 3, the artery is terminal, local anæmia is complete, and bloodless necrosis ensues; 4, the artery is terminal, but regurgitation of blood from neighbouring capillaries or veins leads to the formation of a hæmorrhagic infarct.

(iii.) **Causes of Ischæmia.**—(1) *Embolism.*—Such effects as have been described above may be brought about by a variety of causes, the most common of which during life are embolism and thrombosis. Embolism occurs when some substance formed elsewhere is transported by the blood-stream and lodged in an artery. As a rule, an embolus is arrested at a point where the lumen of the artery becomes narrowed after giving off a branch of more or less considerable size; it then obstructs either the main vessel or the branch. Sometimes, however, when the main vessel bifurcates into two vessels of equal or nearly equal diameter, as at the bifurcation of the abdominal aorta, the embolus " rides " on the bridge between the two branches and immediately, or by reason of subsequent thrombosis, occludes both of them. A consideration of the circulation shows that an embolus of a systemic artery must have been formed either in a larger systemic artery or in the left cavities of the heart or in the pulmonary vein, unless it be so small as to have passed through the pulmonary capillaries, when it might have been formed anywhere; usually it is a portion of a vegetation on a diseased cardiac valve, or a portion of a thrombus that has been formed in the left auricular appendix. An embolism of the pulmonary artery, on the other hand, must have been formed either in the right cavities of the heart or in the systemic veins; the larger pulmonary emboli are commonly formed as thrombi in the uterine sinuses after parturition, the smaller pulmonary emboli are commonly portions of thrombi formed in the right auricular appendix. An embolism of the portal vein must have been formed in the portal tributaries.

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[1] In the particular experiment which he gives, by over 50 per cent.

*Pulmonary Embolism and Infarction.*—Certain points connected with pulmonary embolism and infarction call for special discussion.

When a large embolus obstructs the pulmonary artery or any branch of the first or second magnitude, the symptoms produced are very severe, and the case frequently ends fatally in a few minutes. The effects of such an embolism are, of course, the same as those which would be produced by ligature of the same artery. Ligature of such a branch can be easily carried out in the lower animals, and it is certain from analogy that pulmonary embolism, when so large a branch as those we are considering is involved, leads to an enormous rise of blood-pressure in the systemic veins, acute distension and dilatation of the right ventricle, and a rapid fall in aortic blood-pressure due to diminution in the output of the left ventricle. These conditions readily explain the pain, agonising dyspnœa, cyanosis, and rapid, quickly-failing pulse that clinically characterise a case of "pulmonary embolism."

But an embolus is not generally of sufficient size to obstruct a branch of the first order, and, as we have already seen, the blood may be cut off from a very considerable portion of the pulmonary vascular area by ligature of vessels, without the production of greater results than a small rise in pulmonary blood-pressure. Smaller emboli, therefore, such as those which are dislodged from thrombi formed in the right auricular appendix during the later stages of mitral regurgitation, do not lead to any circulatory disturbances of importance. Nevertheless, they are not without their effects, for the branches of the pulmonary artery are terminal, though perhaps in a modified sense.

Embolism of a small branch of the pulmonary artery differs from embolism of a terminal artery, such as a lenticulo-striate branch of the middle cerebral artery or a branch of the renal artery, in two important respects: 1, it never leads to a bloodless or almost bloodless necrosis; 2, in some cases, experimental as well as clinical, an embolism may be found, in front of which the tissues have undergone no recognisable modification. With regard to the first point, it is clear, bearing in mind the copious supply of the lung with wide capillaries, that the formation of a bloodless necrosis should not be expected, but, on the other hand, the formation of an infarct. Moreover, partly by reason of the freedom of capillary anastomosis, partly from the excessive distension of the ill-nourished capillary walls, and partly from the increased pulmonary pressure, especially on the venous side, obtaining in mitral regurgitation, one would expect the regurgitation from the neighbouring capillaries and veins into the conical mass of tissue normally supplied by the obstructed artery to be greater than under similar conditions elsewhere in the body. And, actually, in the lung conical masses of tissue are to be found under certain conditions which are exquisitely "hæmorrhagic infarcts." But that these conical masses of tissue engorged with blood are "infarcts," in the same sense as the conical mass of altered tissue found after an embolus has lodged in one of the branches of the renal or splenic arterioles is an infarct, is a matter which is open to dispute.

In the first place, the possibility of embolism without the occurrence of circulatory or nutritive disturbance in the tissue supplied by the obstructed pulmonary artery constitutes a difficulty. It has been shown by Litten amongst others that the branches of the pulmonary artery, though they are terminal as regards other branches of the same artery, nevertheless form good anastomoses with the bronchial, pericardial, and mediastinal arteries which are not of pulmonary but of aortic origin. He showed that these systemic arteries could well maintain the nutrition of parts whose blood supply had been cut off by embolism of their particular branch of the pulmonary artery. Though Litten did not deny the embolic origin of hæmorrhagic infarct in the lung, but only differed from Cohnheim in regarding the systemic arteries mentioned as the source of the stagnant blood in the infarct, whereas Cohnheim regarded it as being due to regurgitation from the pulmonary venules and capillaries in the neighbourhood, it is obvious that the possibility of embolism in the lung without infarction, raises the doubt whether embolism and the conical congested masses in the lung commonly known as hæmorrhagic infarcts stand to one another as cause and effect.

In the second place, Virchow long ago pointed out that the branch of the pulmonary artery which normally supplies the affected tissue is only in a small proportion of clinical cases found to contain a solid occluding mass. And even in those cases in which such a mass is actually found, it is difficult, if not impossible, to decide whether the occluding mass is embolic and the cause, or thrombotic and the result.

In the third place, an appearance similar in every respect to a "hæmorrhagic infarct" is produced in the condition known as "pulmonary apoplexy," in which rupture of a small blood-vessel takes place into a bronchiole and the effused blood fills the alveoli with which the bronchiole is in connection. It might be objected that after embolism the blood which forms the "hæmorrhagic infarct" must be confined principally if not entirely to the capillaries, whereas in pulmonary apoplexy the blood occupies a space normally filled with air, but such an objection cannot be sustained in face of the undoubted fact that the blood, even in a renal infarct, does not remain confined to the capillaries but passes through their disorganised wall. Macroscopically and microscopically the appearances of a pulmonary apoplexy are identical with the appearances that might be expected to obtain (and which, it is allowed by those authors who adhere to a belief in the embolic view, actually do obtain) if a portion of the lung became the seat of infarction. The sole exception consists in the fact that in the latter case one might reasonably expect to find an occluding plug in the artery.

For these reasons it is maintained by some authors, amongst whom Hamilton in this country and Grawitz in Germany may be mentioned, that the so-called "hæmorrhagic infarct" has no foundation in fact, and that it is nothing more than a pulmonary apoplexy. Grawitz investigated whether infarctions in which occluding plugs could, and could not, be found, showed differences in structure, but though he examined fifty cases he was unable to discover any difference whatever. Experimentally he found that no infarction as described either by Cohnheim or Litten is the result of occlusion of a branch of the pulmonary artery, that engorgement arises neither from veins nor from collateral arterial anastomoses, and that the "infarction" in the lung is absolutely different in appearance from infarction in either kidney or spleen. He holds that the process begins with an inflammatory congestion and new-formation of minute vessels in the walls of the bronchioles; these vessels, by reason of the exudation which they pour out in the ordinary course of inflammation, induce cough, whereby the inflammatory process is kept up and the vessels are ruptured, pouring the blood into the alveoli; a vicious circle is thereby induced and the "hæmorrhagic infarction" increases in size. Even in those cases in which the branch of the pulmonary artery is found to be occluded, he denies that the plug is embolic or the cause of the condition, for he found that occasionally the newly-formed blood-vessels in the wall of the bronchiole do not rupture into the lumen of the bronchiole but into the loose connective tissue that lies between the bronchiole and the corresponding branch of the pulmonary artery. The effused blood then forms a hæmatoma, which projects into and partially occludes the blood-vessel. This projection, together with the fibrin which is deposited on it from the blood in the manner shortly to be described, at length completely occludes the vessel, and at the autopsy is mistaken for an embolus.

The matter is therefore uncertain, but I think that a solution of the question is aided by the fact that if microscopic sections be stained appropriately, in some cases micrococci are found at the centre or near the apex of the wedge-shaped area which is yielded by the section of the cone. It is known that in ulcerative endocarditis portions of microbe-bearing vegetations are frequently carried to the spleen and kidney, and there form infarcts in which at the centre or apex the existence of bacteria may be microscopically demonstrated. Now the cases in which micro-organisms are found in the conical masses of lung tissue under discussion are especially those in which some bacterial process, usually of a thrombotic and suppurative type, is going on in one or other of the systemic veins, and the inference is that the pulmonary changes in such cases own a common pathology with the renal and splenic changes in cases of ulcerative endocarditis. We may, therefore, provisionally conclude that, where micro-organisms are demonstrable, we certainly have to do with embolism and true hæmorrhagic infarction. Where no micro-organisms are demonstrable, it is uncertain whether the case is one of true infarction or one of pulmonary apoplexy. But if the foregoing provisional conclusion be accepted, the probability is increased that at all events some of the aseptic conical masses in the lung are true infarcts, especially as, in the diseases in which they occur, the right auricle usually contains an abundance of thrombus from which portions might be broken off.

(2) *Thrombosis.*—Thrombosis consists in the separation of fibrin from the blood, and is dependent upon the same causes as those which lead to coagulation. Apart from alterations in the constitution of the blood modifying the rapidity with which coagulation takes place (and these will be considered later), fibrin is deposited upon the wall of the heart or of a blood-vessel *whenever the nutrition of the endothelium covering that wall is impaired.* In the case of blood-vessels such a condition is obviously induced by a

ligature which severs the intima in its whole circumference at one point, by atheroma except in its earliest stages, and by inflammation.

But in addition to these more obvious changes affecting the endothelium, the nutrition of the endothelium suffers, and fibrin is deposited, whenever the velocity with which blood passes through the heart or vessels is greatly diminished for any length of time. This depends upon the fact that the intima, including the endothelial cells, unlike the rest of the vessel wall, derives its nutriment from the blood in the lumen of the vessel, and not from that conveyed by vasa vasorum. In most cases such a diminution in velocity of blood-flow is the proximate cause of the thrombosis. Thus, in the heart the circulation is slowest in the appendices auriculæ, behind the flaps of the auriculo-ventricular valves, and between the columnæ carneæ. Normally, it is rapid enough even here to maintain the nutrition of the cardiac endothelium, but when old age or wasting disease or any lesion of the valves has impaired the musculature of the heart, and it is no longer able to maintain the circulation at its normal velocity, the endothelium in these situations suffers first, and to the greatest extent, and it is just in these situations that thrombi are found. For the same reason thrombosis more commonly occurs in veins[1] than in arteries. So also absence of endothelium and diminution in velocity of blood-flow account for the deposit of fibrin upon the wall of an aneurysm.

But diminution in the velocity of blood-flow through the arteries is not only the result of changes which impair the musculature of the heart, it is also caused by diminution in the calibre of the arteries themselves. Hence, it is clear that thrombosis will most readily occur in arteries when both factors, cardiac and vascular, are in operation together. This obtains typically when extensive arteritis deformans is present, for it has already been shown that the heart in such cases is weak, dilated and flabby, and the arterial condition is one of extreme stenosis. The effects, too, of thrombosis in such cases are proportionately great. For the pathological importance of occluding an artery depends entirely upon the number and size of the collateral branches, and since in arteritis deformans the collateral branches are not only smaller than the thrombosed artery, but are themselves also affected by the calcareous and cardiac changes, it follows that the establishment of a sufficient collateral circulation is highly improbable, and that the thrombosed artery, so far as the nutrition of the parts below is concerned, must be regarded as terminal. And the clinical aspect corroborates this view, for the parts below become bloodless and undergo gangrene. Gangrene thus induced may involve a small or a large area, but the area involved corresponds accurately to the field supplied normally by the artery and its branches, up to and including the seat of thrombosis.

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[1] Another reason for the frequency of venous thrombosis lies in the thinness of the wall of veins, which allows them more easily to transmit to their endothelium any inflammatory process going on in their neighbourhood, whether it be in the sheath of the vessels or in lymphatics or in surrounding tissues of other kind.

Besides accompanying arteritis deformans, thrombosis of arteries is also frequently dependent upon the syphilitic change known as "endarteritis obliterans." In this condition changes take place in the intima of the small arteries, especially those of the brain, which lead to localised stenoses of the vessels. The syphilitic change does not of itself actually occlude the lumen, and to this extent its name is misleading; the final occlusion is due to thrombosis of the ordinary kind.

Arterio-sclerosis, when unaccompanied by the atheromatous and calcareous changes which not infrequently supervene later, is not a common cause of thrombosis, though the narrowing in calibre of the small arteries, which characterises the condition, must tend towards producing a diminution in velocity of blood-flow in the stenosed arteries. This absence of thrombosis, no doubt, depends upon the fact that the heart is hypertrophied in arterio-sclerosis, and that the tendency towards retardation at the distal end of the arterial system is counterbalanced by an increase in velocity imparted at the proximal end.

(3) *Other Causes of Ischæmia.* — Besides embolism, thrombosis and similar conditions, such as ligature and pressure from without by tumours, etc., other causes may lead to a diminution of the calibre of arteries. Some of these seem to act locally, others by way of the vaso-motor centre in the medulla oblongata.

Among the former may be mentioned cold, and such drugs as digitalis, ergot,[1] hamamelis, acetate of lead; among the latter, mental causes, such as fear, and perhaps such a drug as strychnine.

In this connection the morbid conditions known as ergotism, pellagra, and Raynaud's disease are of importance.

Ergotism is produced by the consumption of rye that has become infected by the fungus *Claviceps purpurea*, and the vascular symptoms, with which alone we are concerned, are brought about by the marked constriction of the muscular coat of small arteries throughout the body, which the essential constituent of ergot induces. The constriction is so great, and affects the small arteries so generally, that collateral circulation is greatly impeded if not completely cut off, and the parts supplied by the smaller arteries frequently undergo a gangrene, which in all its characters resembles the senile gangrene that is associated with arteritis deformans.

Pellagra, a disease which occurs in Italy, Roumania, the south of France, and in Spain, and is due to the consumption of certain kinds of maize, is not so obviously associated with vascular changes as ergotism, and the symptoms are more exclusively of a nervous type. But since, in pellagra, cuticular disorders, consisting in redness (pellagral erythema), desiccation, exfoliation of epidermis, suppuration and other inflammatory or sub-inflammatory conditions, accompanied by local death of the skin, are amongst the most prominent symptoms, it is reasonable to suppose that vascular changes are produced by the abnormal chemical constituent in the maize, and that at some time or other those vascular changes consisted in arterial constriction. That this is the case, however, cannot be absolutely affirmed. The actual substance that causes pellagra is not known. The kinds of maize which induce it are infected by the fungus *Reticularia ustilago*. But as pellagra only occurs along with consumption of infected maize, and not with consumption of other kinds of grain attacked by the same fungus, the question is more complicated than appears at first sight.

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[1] Since ergotism is accompanied by nervous symptoms it is possible that ergot acts on the blood-vessels also by way of the vaso-motor centre.

Raynaud's disease is seen in three grades of intensity according to the degree to which the parts supplied by the constricted artery are affected; these are known as local syncope, local asphyxia, and local or symmetrical gangrene. The appearances met with in this disease are all direct or indirect results of arterial constriction; in local syncope one or more fingers or toes may become completely anæmic, leading to the condition known as "dead finger" or "dead toe," and if this condition persists for any length of time it is followed by either an intense cyanosis or a gangrene. These changes are exactly similar to those which may be experimentally produced in the ear of a rabbit by tying a ligature tightly round the root and thus cutting off temporarily its blood supply. A curious point about Raynaud's disease is that it is characterised by a more or less complete symmetry. It usually affects parts whose circulation is carried out by small vessels, such as fingers, toes, tips of ears; whether it also affects the small arteries of internal organs, *e.g.*, the kidney, is uncertain. The ultimate cause of the condition is quite unknown, but the facts that the local changes are entirely due to contraction of the arterioles, which after a time may pass off, that it occurs in different parts of the body, and that in some cases the nerves of the limbs have been found affected by inflammatory changes (peripheral neuritis), seem to indicate that the cause of the diminution in calibre of the arteries is nervous. But whether the constriction is due to efferent impulses descending from the medulla oblongata or to action of a blood whose constitution is altered upon the local mechanism, it is impossible to say.[1] Ehlers, indeed, questions whether Raynaud's disease is not in reality ergotism.

(iv.) **Effects of Temporary Ischæmia.**—The modifications of tissue that we have hitherto considered are brought about if the obstruction to the artery is complete and definitive, or at all events if it acts for a length of time which varies according to the nature and vitality of the tissue which is affected, but which in any case extends to several hours. But under certain conditions the obstruction is removed before it has existed for a sufficient length of time to produce in the tissues the complete changes which it would have produced had it not been removed. That the results of obstruction under these circumstances may be very different is indicated by the fact to which reference has been made above, that in Raynaud's disease the tissues may suffer in three different degrees—anæmia, congestion, and gangrene. We have already seen that blood may enter a mass of tissue whose blood supply has been cut off and cause infarction, but it reaches the part by circuitous routes: the conditions we are about to discuss occur when the blood again reaches the part by the normal route. It may readily be inferred from the nature of the causes which lead to complete occlusion that this removal of the obstruction is rare; an embolus, thrombus, or tumour is not removed within a few hours of its commencement to occlude an artery. Hence the results to be described occur only in special cases.

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[1] Bervœts (*Nederl. Tijdschr.*, 1894, p. 225) found experimentally that extirpation of the sciatic nerve causes in the posterior tibial artery atrophy and degeneration of the nuclei of the muscular coat in its outer part, swelling and new formation of nuclei in those muscle-cells nearer the lumen of the vessel. The changes are progressive. Section of the nerve, therefore, is followed by a progressive new formation of muscle-cells; this may or may not break through the elastic lamina. This modification of the media may explain why the contraction of arterioles in Raynaud's disease leads to more serious results than contraction of normal vessels, and why the various kinds of necrosis occur more commonly after "intoxication-diseases," which are apt to bring peripheral neuritis in their train, and which impair nutrition of the tissues.

If a ligature have been placed round a terminal artery, or for surgical purposes a bandage placed round the arm or leg, if a tight ring have been slipped over the finger or penis, if cold, as in frost bite, or nervous causes, as in Raynaud's disease, have arrested the circulation through a part by producing, in one way or another, cessation of arterial flow, the cause of obstruction may be removed at some variable time after it commenced to act. Now, one point is clear at the outset, and it is that collateral circulation in all the examples given is an impossibility during the period of obstruction, and therefore during that period the part distal to the obstruction suffers in the same way and to the same degree as it would have suffered had it been supplied by a terminal artery.

The results observed in such cases depend upon the vitality of the tissue and the time that elapses between the application and the removal of the obstructing cause. Thus, in the dog, anæmia of the kidney produced by experimental occlusion of the renal artery, and maintained for an hour, is followed on removal of the obstruction by anatomical and physiological changes far exceeding those which follow when anæmia involves the hind leg for the same length of time. But in the leg itself, though removal of an elastic bandage with which complete anæmia has been produced, one hour after its application, is followed by no ill effects, if the removal be delayed until 4–5 hours have elapsed from the time of application, the tissues of the limb with certainty undergo profound nutritive changes, and these changes may end in gangrene of the whole member.

The more profound changes which occur in the tissues after the release of an artery *when it has not been obstructed sufficiently long to cause death of the part*, depend upon two causes. In the first place, it is a fundamental law of physiology that anæmia is followed by congestion, and the cases before us form no exceptions to the rule. The manner in which this congestion is brought about is considered elsewhere, but there is no doubt that it is accompanied by dilatation of the artery and its branches, and by increased exudation from the capillaries and veins. In the second place, as the result of prolonged anæmia, the nutrition of the vessel wall suffers, so that along with the onset of congestion, diapedesis of red blood-corpuscles or actual rupture and extravasation of blood occurs.

The interaction of these two factors leads to an accumulation of exudation and red blood-corpuscles in the inter-capillary spaces which raises the inter-capillary pressure, and this, aided by alteration of the capillary wall itself, interposes an abnormal resistance in the way of the capillary circulation. Consequently, the blood travels more slowly through the tissues, gives up a greater amount of oxygen than normal in its transit through the capillaries, and becomes intensely venous. If the exuded fluid and corpuscles are limited in amount, they are removed in course of time, and the part returns to its normal condition. But if they are excessive in amount, the pressure which they exert finally obliterates the circulation through the part, and it passes into a condition of moist gangrene.

If the cause of obstruction be not removed till two or three days have elapsed from the time when it produced complete cessation of arterial flow, removal of the obstruction leads to no further alterations. For the tissues on the distal side of the obstruction are already dead and blood does not enter them at all, or only penetrates for a short distance. The actual changes seen in the part are therefore independent of removal of the obstruction, and vary according to the circumstances under which complete cessation of arterial flow was brought about. In particular, they vary according to whether the cessation of arterial flow was brought about directly, or indirectly by way of venous congestion. We shall return to this subject when considering gangrene.

A beautiful clinical example of the effects which temporary arterial obstruction may produce upon a part is offered by Raynaud's disease. While the obstruction lasts the part is bloodless, pale, and cold (local syncope). With removal of the obstruction by relaxation of the arterial spasm, and as a result of the arterial congestion which necessarily follows on the antecedent anæmia, the part becomes red, hot, and somewhat swollen; later, along with increase of the swelling the part may become cold and cyanosed (local asphyxia). If moderate, local asphyxia may disappear, and then the part returns to its normal condition, but if the exudation, which is the essential cause of local asphyxia, exceed a certain amount, death of the part supervenes (local gangrene).

(v.) **Septic and Aseptic Obstruction of Blood-vessels.**—The ultimate changes which the tissues undergo as the result of an obstruction to their supply of blood, depend not only upon the conditions that have already been discussed, but also upon whether those changes take place in the presence or in the absence of pathogenetic micro-organisms—in other words, whether they are septic or aseptic.[1]

If the cause of obstruction is aseptic, then the results are aseptic, and such as have been given. The tissue that dies in the case of obstruction of a terminal artery undergoes degenerative changes, which end in the formation of a denser or softer innocuous mass containing numerous fat globules and more or less blood-pigment. This mass, according to its size, position, and consistency, may either remain unaltered, or be absorbed, or become surrounded by a capsule of fibrous tissue, or be replaced by fibrous tissue, or undergo subsequent putrefactive changes (gangrene) and be cast off.

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[1] The special case in which an embolus consists of a portion of a malignant tumour will be discussed in Chapter XII. The physical constitution of an embolus, whether it be solid, such as fibrin or solid paraffin, liquid, such as fat, or gaseous, such as air, really modifies in no essential point the effects of embolism upon the tissues.

But if the cause of obstruction to an artery be septic, the matter is different, for not only are the mechanical and degenerative effects of simple obstruction produced, but over and above them there supervene other changes due to the action of pathogenetic micro-organisms upon the wall of the artery. These arterial changes in their turn involve surrounding parts, and tissues, other than those which were primarily deprived of blood, suffer. How different the results are with septic and aseptic obstruction is shown by the fact that, whereas aseptic occlusion of a freely anastomosing artery is without effect upon the nutrition either of neighbouring parts or of those parts supplied by the obstructed vessel, septic occlusion of the same artery, on the contrary, is always followed by more or less marked pathological changes of the parts immediately surrounding the seat of occlusion. These latter, by impeding the collateral circulation, may ultimately involve in destruction a far greater mass of tissue than would have been destroyed had the obstruction been aseptic and the occluded vessel terminal. *Mutatis mutandis*, the same is true in the case of septic and aseptic obstruction of veins.

All these pathological terminations of obstruction, however unlike one another at the first glance, with the sole exception of that one in which the disorganised cone of tissue remains unaltered and unabsorbed, are brought about through the medium of processes which are inflammatory or are frequently seen in inflammation, and the manner in which they are brought about will be left for discussion along with that subject.

**V. Local Hyperæmia or Congestion.**—Local hyperæmia or congestion may be dependent upon either an increased supply of blood to a part or a diminished removal of blood from a part.

It may therefore be brought about by dilatation of arteries or by obstruction of veins. The forms of congestion thus induced are so different that they must be discussed separately.

A. **Arterial Congestion.**—Arterial congestion is due either to active nervous influence or to removal of the normal tone of the smaller arteries by paralysis of their vaso-motor mechanism. Hence it may be either "active" or "paralytic."

Active congestion may be brought about through the medium of the central nervous system; examples of this variety occur in salivation and sweating due to mental emotions, and possibly also in "blushing." More commonly, however, it is caused by the direct action of some stimulus upon the peripheral nervous mechanism, as in the case of the arterial dilatation brought about by the application of gentle heat.

Uncomplicated active congestion is but rarely met with in pathology; it occurs in the remaining organ when one of a pair has been removed or from any cause has become functionless; it occurs where hypertrophy is taking place; perhaps it occurs when the vessels forming a collateral circulation dilate after occlusion of the main vessel. But even in these cases it is more justly spoken of as physiological than as pathological. It is not until we have passed the indefinable line separating physiology from pathology that active congestion is frequently met with, and then it is not uncomplicated, but, on the contrary, invariably complicated by the presence of some one or other of the processes which go to make up the complex condition known as "inflammation."

The causes of paralytic congestion are sometimes very obvious: the spinal cord or a nerve may be pressed upon by a tumour or may be actually divided by some injury, or reflex inhibition of the vaso-motor centre may be brought about by stimulation either of a large number of afferent nerves, or the afferent nerves of an important organ as in the condition known as "shock." Paralytic dilatation of arteries is also induced by drugs such as the inorganic nitrites, the organic nitrates of the fatty series, chloral, amyl nitrite, nitroglycerine, and curare, all of which act peripherally either upon the muscular coat of the artery or upon the local nervous mechanism (curare) or upon both.

It is also produced by drugs such as anæsthetics and narcotics, which depress the vaso-motor centre along with the rest of the brain and cord and therefore may be said to act centrally. Dilatation of this kind acts from within the vessel and through the blood, it is therefore general; for a dilatation to be local, the drug must either act from without, *e.g.*, the whole class of rubefacients, or if acting from within, it must have a special selective action upon one particular part or organ. An example of the latter class is afforded by cantharides, which, given internally, produces an intense congestion of the kidney.

Paralytic arterial congestion must be kept distinct from active arterial congestion, not only by reason of the difference which obtains in their modes of production but also by reason of the fact that, unlike the physiological process of active congestion, paralytic arterial congestion is essentially pathological and has no strict counterpart in health. Moreover, the effects of the two kinds of arterial hyperæmia are different, as are the courses which they run. Active congestion occurs in company with increased functional activity and increased metabolism, paralytic congestion occurs along with diminished functional activity and probably, therefore, with diminished metabolism, though the latter point is not so certain; active congestion is commonly unaccompanied by any alteration in the mean arterial blood-pressure, paralytic congestion is frequently associated with a fall in the blood-pressure; active congestion is accompanied by an increase in the flow of lymph from the part, paralytic congestion, at all events for a time, is accompanied by no increase in the flow of lymph, and in some cases even a diminution is observed. Nevertheless, they have certain characteristics in common. Both varieties lead to swelling and redness of the part from the increased amount of arterial blood which it contains; both lead to an increase in the velocity of the blood-stream through the part owing to diminution of the resistance between the heart and the capillaries; both lead to increased warmth of the part, if it be superficial, from the shorter time during which heat can be lost by radiation from a given volume of blood; both, if prolonged, lead to hypertrophy of the arteries by reason of the increased nutriment which reaches the vessel walls through the dilated vasa vasorum; and in both the increase in calibre of the vessels may be such that the pulse-wave is not obliterated in them, but passes through to the veins.

In spite of the differences and because of the similarities between active and paralytic congestions, it is frequently difficult to determine which of the two is present, while, even if it be finally concluded that the congestion is active, it is by no means easy to decide whether the dilatation of arteries is primarily due to action of the central or primarily due to action of the peripheral nervous mechanism. Moreover, strictly speaking, *active* dilatation of vessels cannot occur at all, unless it be brought about by the action of vaso-dilator nerves, and even then all dilatation of whatever kind consists in the removal of arterial tone, and, therefore, comes very close to a paralytic process. But since one is forced to recognise that the results of an otherwise indistinguishable dilatation of arteries differ according to the circumstances under which that dilatation occurs, it is necessary to have distinctive terms, and therefore the terms "active" and "paralytic" are preserved.

The causes of active congestion practically resolve themselves into the causes of increased metabolism, and of these functional activity and warmth [1] are the chief. As to the mode in which the local dilatation of arteries is brought about, we can only have recourse to hypothesis. We know that increase of function and increase of blood-supply go hand in hand, and since increase of function implies increased formation of tissue waste-products, it is reasonable to expect that these are not without their influence upon the processes at work. Gaskell showed that the tonicity or degree of contraction of the frog's heart and of arterial muscle is very closely bound up with the reaction—alkaline or acid—of the fluid which bathes it. With very weak acids an atonic or dilated condition is induced, with weak alkalies a tonic or contracted condition, and changes from atonicity to tonicity and *vice versa* may readily be produced by changing in the appropriate manner the reaction of the bathing-fluid. He suggests that the dilatation of the blood-vessels which accompanies functional activity is dependent upon the acidity, or rather the diminished alkalinity, of the lymph, which leaves the part in action, and which, on its way towards the lymphatics, is contained in lymph spaces that surround the arterial wall. In the case of voluntary muscle, at all events, it is known that functional activity is accompanied by the formation of $CO_2$[1] and an acid substance, possibly sarcolactic acid. So that there is a certain amount of evidence in favour of the view that local active dilatation of the arteries is due to local influences upon the local mechanism. Nevertheless, so many examples of functional activity of glands are known which are clearly under the control of the central nervous system, and in which the increased blood supply is a necessary preliminary factor to the appearance of an increased secretion (*cf.* sweat, urine, saliva), that one hesitates to regard active hyperæmia as being completely dependent upon local causes.

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[1] It is clear that we are speaking here only of local metabolism; the general metabolism of the body is diminished by external warmth and not increased.

It has already been stated that active congestion is commonly unaccompanied by any change in the mean arterial blood-pressure; the reason of this lies in the fact that the area which is the seat of active congestion is, as a rule, sufficiently small for compensatory constriction of the arterioles in other parts to take place. The effect of paralytic congestion upon the general blood-pressure varies according to the extent of the area over which the arteries are dilated. If the sciatic nerve be divided and the leg becomes congested, large though the area is, it is nevertheless not so great but that, by coincident constriction of arterioles in other parts (particularly in the splanchnic area), the mean blood-pressure can be maintained, and this actually occurs. But if the splanchnic nerves be divided, the vascular area affected is so enormous, and the amount of blood which collects in the dilated vessels is so great, that no amount of vaso-constriction in other parts of the body is able to compensate for the local hyperæmia in the abdomen, and hence the blood-pressure falls. Consequently the effects upon the mean blood-pressure of an injury to, or of a tumour in, the spinal cord depend upon whether it is situated above or below the region which gives origin to the splanchnic nerves; if it be situated above, it cuts off constricting impulses passing from the vaso-motor centre to the abdominal arteries, and the blood-pressure falls; if it be situated below, the splanchnic vessels are exempt, and the blood-pressure remains at its normal height. The action of drugs upon the blood-pressure shows similar differences; those drugs which act generally, *e.g.*, amyl nitrite, etc., produce a fall in blood-pressure, those which act locally, *e.g.*, rubefacients, leave the general blood-pressure unaltered.

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[1] Morley Fletcher's experiments, shown at a meeting of the Physiological Society in May 1897, throw some doubt on this statement.

B. **Venous Hyperæmia or Congestion.**—Owing to the absence of vaso-motor control of veins, or its insignificance as compared with that of arteries, venous congestion is not obviously due to either active or paralytic dilatation of the vessel walls. It appears to be solely the result of a passive distension of the veins behind some obstruction, and for this reason is frequently called "passive" congestion. In venous as in arterial congestion, the capillaries are more than usually full of blood, but in this case the part though swollen is not red but purple, usually not hot but cold, and the blood-flow through it not more rapid but less rapid than normal.

The circulatory changes in passive congestion can be very well studied microscopically in the tongue or the swimming-web of the frog. If a ligature be tied around the thigh of a frog close to the pelvis sufficiently tight to constrict the veins but not to obstruct the artery, the following appearances are seen. It is noticed after a short time that the veins of the swimming-web are dilated and distended with blood, that a larger number of capillaries is visible in any given field of the microscope than normal, and that their diameter is increased. Whereas only one corpuscle was formerly able to traverse the capillary at a time, and that, too, travelling in the direction of its long axis, now two or three corpuscles may be seen travelling abreast. It will further be noticed that the velocity of the blood-flow is diminished; in the normal condition the blood flows so rapidly through the arteries that the outline of the individual corpuscles cannot be seen, and through the veins with a rapidity that is scarcely less marked. But now the individual corpuscles in arteries and in veins can be distinguished if the congestion be not too severe, and in the capillaries a corpuscle remains for a very appreciable length of time. As time goes on distension of the vessels increases[1] and the blood flows more and more slowly, with the result that the division into axial and plasmatic portions is lost and the red blood-corpuscles come to lie against the vessel walls. When the condition is very advanced, the red blood-corpuscles are pressed so closely against one another that they lose their outline, and the vessel with its contents appears to be converted into a solid homogeneous red cylinder. At this moment there is seen on the outer side of the walls of capillaries and small veins a number of protuberances, which gradually increase in size and finally assume the characters of red blood-corpuscles. The number of red blood-corpuscles that may be extruded from the blood-vessels by this process of diapedesis varies according to the degree and duration of venous obstruction. In the dog at times it is so considerable as to cause the lymph leaving the part to take on a bloody appearance, and even with minor degrees of obstruction it is commonly found on microscopical examination that a certain number of red blood-corpuscles is being carried away in the lymph. To the question of the lymph-flow in passive congestion we shall return later when dealing with the subject of œdema, but it may be stated here that when venous obstruction has been in existence for some time the lymph-flow is increased.

The circulation through a part whose veins are obstructed goes on, though with increasing slowness, until the pressure in the veins is nearly equal to the pressure in the arteries; before the blood-flow actually ceases it shows for a time an intermittent forward movement, owing to the fact that the obstruction is so great that it can only be overcome during the height of ventricular systole.

Venous congestion does not modify the aortic blood-pressure. For the increased pressure in veins and capillaries of the part affected is not transmitted backwards beyond the small arteries which constitute the peripheral resistance, and cardiac output is unaltered because diminished venous outflow from the part is rapidly met by a diminution in its arterial supply. Nevertheless when the vena cava is obstructed *above* the liver, aortic pressure falls enormously owing to lessened cardiac intake.

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[1] According to Thoma, the calibre of the *arteries* is diminished. He maintains that a diminution in calibre of arteries always accompanies a retardation of the flow of blood in them.

The effects produced upon the tissues by venous congestion largely consist in œdema, and this we must leave on one side for the present, but certain other changes may be noticed. These are of three kinds: 1, a lowering of the general nutrition of the part, rendering it liable to suffer severely from irritants which under normal circumstances would have but slight consequences or none at all; 2, hypertrophy of certain forms of tissue; and 3, diapedesis of red blood-corpuscles.

With regard to the lowering of nutrition in the part, this may vary within very wide limits, from an increased tendency to inflammation or ulceration as the result of small injuries, which accompanies the milder forms of *chronic* venous congestion, to moist gangrene, which accompanies the severer forms of *acute* venous congestion. Hypertrophy is only seen when venous congestion is chronic and it chiefly affects fibrous tissue and epithelial structures. Thus, in the chronic venous congestion of congenital malformation of the heart, the fibrous tissue at the ends of the fingers becomes hypertrophied and the nails become enlarged, leading to the condition known as "clubbing" of the fingers. In the later stages of mitral regurgitation, along with the chronic venous congestion of the liver, spleen, and kidneys, there is found an increase in the amount of fibrous tissue that forms the supporting structure of these organs. In the neighbourhood of a varicose ulcer on the leg, the epidermis is thicker than normal and the hair grows more luxuriantly.[1] Diapedesis of red blood-corpuscles occurs with severe and acute venous congestion, and the amount of blood that is extravasated into the tissues in this manner may be so great as to merit the name of hæmorrhage. If the blood-vessels are, comparatively speaking, unsupported, actual rupture of the vessels may take place, but in diapedesis the red blood-corpuscles are usually regarded as passing through the uninjured walls of the capillaries or veins; to this point we shall return when dealing with the subject of inflammation.

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[1] It will be noticed that it has not been said that these examples of hypertrophy are *caused* by the congestion. Hypertrophy, it is true, is caused by prolonged congestion, but it is a congestion of the active arterial type, which implies an increased amount of nutriment. Chronic venous congestion, though it is accompanied by an increased amount of blood in the part, implies a diminution in amount of nutriment owing to the sluggishness of the circulation and the deficient renewal of blood. It is therefore difficult to associate chronic venous

The causes of venous congestion are such as lead to obstruction of the veins, but one important point must be borne in mind, viz., that the collateral circulation in the case of veins is extraordinarily free. It is not sufficient to ligature the femoral vein in the middle of a dog's thigh in order to produce venous congestion of the paw; such an operation has at most a momentary effect, for the increased pressure of blood in the veins behind the obstruction is sufficient to open up the easily distensible collateral paths that unite the vein below with the vein above the obstruction.[1] But if a ligature be placed with moderate tightness around the whole thigh, and a certain amount of obstruction be placed in the way of the return of blood from the paw through all the possible channels, then venous congestion of the paw results. Hence in disease passive congestion is seen only when venous obstruction is due to central or to extensive peripheral causes. It occurs most commonly along with tricuspid regurgitation, the result of cardiac failure, and then it is general. It is most marked in the dependent parts, owing to the impaired force of the heart, which now is less able than formerly to drive the blood through the veins in a direction opposed to gravity. It also occurs wherever thrombosis obstructs the lumen of many veins: such a condition is found in the portal vein and its branches in inflammation of those vessels, and in the femoral vein in the condition known as phlegmasia dolens. It occurs

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congestion with hypertrophy as cause and effect, though it must be confessed that in the cases before us it is quite as difficult to explain the hypertrophy which undoubtedly obtains in any other manner.

[1] Even ligature of the superior vena cava or of the inferior vena cava below the liver does not produce any effect upon the pressure in the carotid artery of a dog. (Cohnheim, *Lectures on Pathology*, New Syd. Soc., p. 167.)

wherever pressure is exerted upon veins from without, as, for example, by a tight bandage or ring, by an aneurysm or a solid tumour. In many of the cases mentioned, however, the congestion is to be recognised rather by the presence of that œdema which accompanies it, than by an actual overloading of the part with venous blood and a cyanosis.

Before dismissing the subject of congestion, there are two further varieties which must be briefly mentioned. These are (A) the congestion which is brought about by a local diminution of pressure, and (B) the congestion which is known as "hypostatic."

(A.) The congestion which is brought about by a local diminution of pressure is seen in its simplest form when the atmospheric pressure is diminished over some superficial part. Thus it occurs typically in the almost obsolete practice of "dry cupping." The operation consists in holding a cup-shaped glass over the flame of a spirit lamp, whereby the air within it becomes warmed and rarefied, and closely applying it while still warm to the skin of the patient. The air within the cup as it cools contracts, reduces the pressure within the cup below the pressure of the atmosphere, and therefore exposes the tissues which are covered by the cup to a diminished pressure. The distensible skin which is exposed to this diminished pressure expands and becomes sucked up to a certain extent into the cup.[1] Along with the skin the blood-vessels dilate also, and the part becomes red and congested.

Now the difference between this form of congestion and those which we have previously considered consists in the fact that the local diminution of pressure leads neither to an exclusively arterial nor to an exclusively venous congestion, but to a local attraction of blood from all parts, arteries, capillaries, and veins, in which the pressure is greater than it is at the seat of cupping. But the congestion which is produced in this manner, or by applying suction with the mouth to a soft part, remains for some time after the pressure over the part has returned to normal, and hence one must conclude that there is something more in the congestion than the simple process given above. The small hæmorrhages that are frequently seen, especially in the neighbourhood of the hair-follicles, depend upon actual rupture of some of the less supported capillaries, and this is certainly due to the diminished pressure on one side of them, but the general congestion (which may last for an hour or more, and which is not inflammatory) must be regarded as due to a local paralysis of the arterioles. For the part is warmer than elsewhere in the neighbourhood, and the circulation through it is more rapid than usual, as can be determined by the instantaneous return of redness after removal of intra-vascular blood from the part by pressure with a finger; anæmia of the surrounding but unaffected parts produced in the same way does not give place to the normal colour after removal of the finger until an appreciably longer interval of time has elapsed.

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[1] Strictly speaking, the skin is of course not "sucked" up by the diminished pressure within the cup but "pushed" up by the atmospheric pressure outside.

A process that is essentially the same comes about in the body when a part has been subjected to increased pressure for some length of time and the increased pressure is suddenly taken off. This occurs, for example, in a hydrocele, where the tunica vaginalis of the testis is the seat of an effusion that produces a considerable amount of pressure on the walls of the sac. On making a small puncture in the sac, as in the usual method adopted for emptying it, the fluid is expelled with some force. The sudden diminution of pressure produces a congestion of the blood-vessels running in the wall of the sac and hæmorrhage into the sac not infrequently occurs. The same is seen when fluid has collected in the abdominal or one of the pleural cavities, or when the abdominal pressure is suddenly diminished by the removal of a large abdominal tumour. The amount of blood that may be diverted from the circulation generally, and from the brain in particular, to fill the dilated vessels is sometimes so great that faintness is produced, and the hæmorrhage which occurs from the congested blood-vessels may be so considerable as to be alarming. It is obvious that these severer symptoms more commonly occur when the abdomen is the seat of operation than elsewhere.

(B.) Hypostatic congestion depends upon the fact that, under the conditions in which it obtains, gravity exerts a greater proportionate resistance towards the flow of blood in the veins than normal.[1] Hypostatic congestion occurs in dependent parts, and is seen when the propulsive power of the heart is diminished, as in old age or at the latter end of severe or exhausting diseases such as typhoid fever. In dependent parts the return of blood to the heart is opposed by gravity, but normally the force of the ventricular systole is such that that portion of the force which passes the peripheral resistance and the capillaries is sufficient to overcome the effect of gravity and urge the blood onwards. When the heart is weakened, this is not the case, and the blood travels towards the heart only during the height of systole, so that the venous flow becomes intermittent; if the heart be excessively weak, actual stagnation in the dependent parts may occur. The cardiac weakness is further aided by the fact that muscular contraction, which is so potent an adjuvant to the venous circulation, is in these very cases reduced to its lowest limits, practically consisting only in the action of the enfeebled respiratory muscles. Owing to the smaller force exerted by the right ventricle, hypostatic congestion occurs earliest and is most marked in the lungs. The stagnation of the blood leads to deficient nutrition of the part, and such changes are produced as are associated with passive hyperæmia and deficient nutrition of the vessel wall, viz., œdema, extravasation of blood, and a tendency to undergo low forms of inflammation. Clinically, hypostatic congestion is of the highest importance, but pathologically, it offers no real difference from the venous congestion which has already been described.

VI. **The effects of Hæmorrhage.**—Sudden variations in the quantity of blood in the body may be regarded from three points of view: either from that of the blood itself, or from that of the tissues which lie outside the blood-vessels, or from that of the heart and blood-vessels. It is from the latter aspect alone that they will be considered here.

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[1] L. Hill finds that gravity is "a cardinal factor" in the circulation, but that its importance varies in different animals. In animals in which the erect position is usual, such as monkeys, and presumably therefore in man, gravity exerts but little disturbing influence, owing to the perfection of compensation that is effected by vaso-motor changes in the splanchnic area, but in four-footed animals compensation is not so effective, and the result of, *e.g.*, the "feet-down" position is that aortic blood-pressure is lowered. This depends upon the fact that, in this position, blood collects in the splanchnic veins instead of entering the right heart. The input of the right heart being diminished, the output of the left ventricle is lessened, and other factors remaining constant, the blood-pressure falls. In the "head-down" position the exact converse obtains.

It is unnecessary to enter here into a discussion of the effects of suddenly increasing the volume of fluid in the blood-vessels, as the subject will need consideration in connection with transfusion. Sudden diminution in the volume of the blood in the body occurs in every case of severe arterial or venous hæmorrhage. The diminution is not produced with so great suddenness when hæmorrhage is from veins, as when it takes place from a divided artery, nor is it common for the loss of blood to be so great in the former case by reason of the lower blood-pressure in the veins, the smaller velocity of the blood-flow, and the greater coagulability of venous blood, factors which aid in hastening the onset of that thrombosis which is the natural means whereby hæmorrhage is arrested. The suddenness with which loss of blood takes place is of more importance in this connection than mere quantity. In hæmophilia, for example, the loss of blood by gradual oozing from an abraded surface may be so great as to induce extreme blanching of the patient, but circulatory changes such as supervene on severance of the femoral artery or in post-partum hæmorrhage are conspicuously absent.

It is well known that the general blood-pressure is not permanently affected by hæmorrhage unless that hæmorrhage be carried to an alarming extent; up to one-third of the initial volume of the blood may be lost, and yet the general blood-pressure remains at its normal level. The pressure, no doubt, falls during the actual period of hæmorrhage, but so soon as it is arrested, whether by natural or by artificial means, the pressure regains its original level. This is brought about because the peripheral resistance is increased by vaso-motor action and the capacity of the vascular area, especially in the splanchnic regions, is diminished; as long as variation in these directions is possible, so long the normal blood-pressure is maintained.

The part played by the arteries in organs and tissues other than that whence the arterial hæmorrhage is taking place is exactly similar to the part which would be played by them if, instead of hæmorrhage, a local arterial congestion was being produced. The blood-pressure is maintained in both cases, but whereas this is beneficial to the whole economy in the case of a local arterial congestion, it is distinctly injurious to the whole economy when hæmorrhage is taking place. For the amount of blood lost per unit of time from a given divided artery depends upon the pressure under which the blood is in the system. The maintenance of the blood-pressure, therefore, is one of the chief causes in rendering the loss of blood that takes place from a large divided artery so great as to be a danger to life. And, indeed, were the blood-pressure to be maintained to the end, hæmorrhage in the case of a large artery would not cease until the last drop of blood had been expelled from the body. That this is not the case depends upon the fact that, when the loss of blood has proceeded to a certain extent, the blood-pressure falls.

But not only does the amount of blood that issues in a given time from a divided artery depend upon the pressure behind it, it is greater than the amount of blood which passed over the same spot in the same time when the artery was undivided. This depends upon the removal of the peripheral resistance in front. The velocity with which the blood-stream flows past a given point in the carotid depends upon the ratio borne by the force of the heart's beat to the peripheral resistance. When the vessel is divided, peripheral resistance, so far as the velocity of the stream over the central end is concerned, is reduced to zero, and, since the blood-pressure elsewhere remains normal and the force of the heart's beat remains normal, the velocity of the issuing stream is greater than was the blood-flow in the undivided artery. Nicolls has estimated mathematically that in man, if the carotid were divided, the blood would spout from the central end of the vessel with a velocity twenty-one times as great as that with which it passes over the same spot in the undivided artery.

The effects of severe hæmorrhage chiefly consist in an altered composition of the blood and in anæmia of the brain: the former will be referred to in its proper place, the latter causes those epileptiform convulsions seen with severe hæmorrhage.

VII. **Venous Pulsation.**—In this and the preceding chapter we have incidentally mentioned the chief variations in the arterial pulse, and have pointed out that in local arterial dilatation a true pulse may sometimes be observed in the veins. Venous pulsation, however, is more commonly met with in pathology under a different set of conditions. It is best seen in the superficial veins of the neck, in cases where there is severe tricuspid regurgitation. The venous pulse of pathology differs from the venous pulse of physiology in two respects at least: the pathological venous pulse is regurgitant and occurs at the cardiac end of the veins where they are large; the venous pulse of physiology is direct, and occurs at the capillary end of the veins where they are small. The venous pulsation that occurs in tricuspid incompetence is at times so forcible that an organ such as the liver, which is close to the heart and contains many veins, may pulsate as a whole.

VIII. **Capillary Pulsation.**—Normally, the pulse-wave in the capillaries is so small, and the velocity with which it travels is so great, that no pulsation is recognisable in them at all, but under certain circumstances the intermittent action of the heart manifests itself in these vessels. It is not here recognised by the sense of touch as it is in the arteries, but by the far acuter sense of sight. During the passage of a pulse-wave over any point, the mass of blood which the vessel contains when the wave is passing is greater than that which exists at the same spot either before or after that moment. Were the arterial walls and the superjacent structures transparent, and the layer of blood not so thick as to cause one uniform depth of colour at the spot, we may assume that a greater or lesser volume of coloured corpuscles would show its presence by an increased or diminished momentary redness in the part. Now the capillaries manifest this transparency of wall and tenuity of the layer of contained blood sufficiently well for change of volume of contained blood to be represented by change of colour. Hence change of colour with the heart's beat, if it be present in the capillaries, may be taken as evidence of the same effect of the heart's beat in them as is the impulse in the arteries. That the capillaries themselves may vary in bulk as do the arteries is possible, but touch is not sufficiently acute to perceive a difference which is often recognised by sight with the utmost facility.

The momentary flushing of a part, the capillaries of which with each heart's beat contain a greater amount of blood than normal, is best observed on the inner surface of the lip, where the epithelium is comparatively thin and the number of capillaries large. If the lower lip be everted and an ordinary microscopic slide be pressed upon it the phenomenon, if present, will become visible. The lip being convex forwards, the amount of pressure applied is immaterial, for though with a greater amount of pressure it is further away from the centre of the area of contact than with a smaller amount, yet a spot can always be found over which the pressure is just sufficient to allow the pulsation to be seen to the best advantage. Occasionally the pulsation is so marked that a part may be seen to flush coincidently with the heart's beat without any artificial aid.

In a typical case of capillary pulsation (viewed by the above method) there is a central area into which no blood enters owing to the pressure of the slide, but at some varying distance from the centre is found an area or narrow zone where the colour becomes intermittently deeper red and paler, and the edge of which seems to be in continuous movement, now encroaching upon, now receding from, the central area of complete anæmia, which lies next it.

Capillary pulsation is essentially a pathological phenomenon; according to the author's investigations, it is almost exclusively observed in cases of aortic regurgitation and in the congested zone surrounding a superficial wound that is covered by a scab. The explanation of the phenomenon in these two cases seems not to be the same.

In aortic regurgitation it appears to be caused in the following way. Every pulse-wave consists of two sets of vibration, one transverse to the direction of the wave, the other longitudinal. The amplitude of the transverse vibration varies directly with the diameter of the vessel through which it is passing, and in the capillaries it is so small, and the velocity with which it travels is so great, that transverse vibrations *never, under any circumstances,* become recognisable in these vessels. The longitudinal vibration of a pulse-wave is practically independent of the diameter of the vessel through which it is passing, but depends upon the ratio between the transverse and longitudinal tensions of the wall. When the pressure is sufficiently high to make the transverse tension of the vessel greater than twice the longitudinal tension (as it is in a normal artery), the longitudinal vibration of the pulse-wave is so small as to be imperceptible whether in arteries, capillaries, or veins. And this helps to account for the normal absence of pulsation in capillaries. But when the transverse tension of the vessel is *less* than twice the longitudinal tension (as it probably is in cases of aortic regurgitation), the longitudinal vibrations of the pulse-waves become perceptible; and since they are not affected in the same way as the transverse vibrations by the diameter of the vessel through which the wave is passing, they show themselves in the capillaries.

When capillary pulsation occurs in the neighbourhood of a scab, it is probable that during diastole an actual recoil of blood takes place from the barrier presented by the scab and the thrombosed capillaries beneath it. At all events, in glaucoma, a condition in which the intra-ocular tension is increased, and in which, therefore, a somewhat similar barrier is presented at the entrance of the vessels into the eye, arterio-venous pulsation may be observed in the vessels coursing over the optic disc; the same phenomenon may be observed if the intra-ocular pressure be artificially increased by pressing on the upper portion of the globe with the finger while the fundus of the eye is under observation.

It must be admitted, however, that the explanation and the significance of capillary pulsation are subjects upon which there is a divergence of opinion. One reason of this is that the phenomenon is sometimes—but rarely—seen under other conditions than those mentioned; the chief of these is excitable action of the heart even when no recognisable disease of any kind is present. Whether in these cases also a small amount of aortic regurgitation occurs, one cannot say, but judging from the fact that excitement sometimes leads to the appearance of a functional systolic murmur connected with the mitral valve, such an explanation is not impossible.

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# CHAPTER V.

## THE PATHOLOGY OF THE BLOOD, WITH ESPECIAL REFERENCE TO THE BLOOD-CORPUSCLES AND THE ANÆMIAS.

*Synopsis.*

I. The Coagulability of Blood :
  (i) Experimental.
  (ii) (iii) Pathological Variations of Coagulability.

II. The Specialised Elements of the Blood :
  (i) The Red Corpuscles.
  (ii) The Colourless Corpuscles.
  (iii) Blood-Platelets.

III. The Anæmias :
  (i) Anæmias in which marked Changes in the Number or Characters of the White Blood-Corpuscles are *absent.*
    A. The Principal Change is a Diminution in the Number of Red Blood-Corpuscles.

III. The Anæmias :
    B. The Principal Change is a Diminution in the Hæmoglobin Content of the Red Blood-Corpuscles.
  (ii) Anæmias in which marked Changes in the Numbers or Characters of the White Blood-Corpuscles are *present.*
    A. Leuchæmia or Leucocythæmia.
    B. Pseudo-leuchæmia.
  (iii) The Varieties of Colourless Corpuscles present in the Anæmias.
  (iv) Sources of Abnormal Blood-Corpuscles in the Anæmias.
  (v) Effects of Anæmia upon the Body.

IV. Leucocytosis and Leucopenia.

The study of pathological changes occurring in the blood is rendered difficult by the fact that of all constituents of the body the blood is perhaps the most unstable. It varies in quantity, in specific gravity, in relative proportion of cells to plasma and even of one kind of cell to another in different individuals, and from time to time even in the same individual. And that, too, without passing beyond the bounds of physiology. No pretence to completeness can therefore be made in the following pages, but an attempt is made to present the salient points of the subject.

I. **The Coagulability of Blood.**—(i.) **Experimental.**—Coagulation of the blood at the present day is known to depend upon the presence of three factors at least, fibrinogen, fibrin ferment, soluble salts of calcium. Concerning the first and second of these, there is no doubt whatever that they are absolutely essential to the process. The importance of a salt of calcium in coagulation was first shown by J. R. Green, and the subject was afterwards investigated closely by Arthus and Pagès, and others. But though there is no doubt that the presence of calcium is highly favourable to the onset of coagulation, it is a little doubtful whether it is absolutely essential. One difficulty in the way of deciding this point consists in the fact that the amount of calcium in question is extremely minute. Thus, in spite of the relative insolubility of calcium sulphate in water, sufficient is taken up for coagulation to be absent or to take place in an experiment upon coagulation according as distilled water or boiled tap water is used in preparation of the fluids to be investigated.

The action of cobra poison—largely, an albumose—upon coagulation of blood is very curious, and raises doubts as to the essential importance of calcium in the process. It was shown by Kanthack, at a meeting of the Physiological Society in 1896, that if 4 mgr. of cobra poison be placed in a test-tube, and a normal rabbit be bled directly into the cobra poison, the mixture remains fluid for days. If the same procedure be adopted, but the rabbit have been previously immunised against cobra poison, the mixture of blood and cobra poison in the test-tube coagulates even more rapidly than normal rabbit's blood without cobra poison. If, however, a trace of serum from an immunised rabbit be added to 4 mgr. of cobra poison, and a normal rabbit be bled into the mixture, coagulation takes place immediately. The last experiment is the more extraordinary in that the trace of immunising serum added is quite insufficient to neutralise the toxic effects of the cobra poison. The coagulation or absence of coagulation in these three cases can hardly be regarded as dependent upon the presence or the absence of a calcium salt.

If to the blood or any other coagulable fluid a small amount of oxalate of potassium (·2 per cent.) or of citrate of potassium

(·5 per cent.) be added, the onset of coagulation may be retarded for an indefinite time, though occasionally, when citrate of potassium has been used, coagulation may occur after weeks have passed. It is generally held, at least in the case of potassium oxalate, that it combines with the calcium normally present in the blood or other fluid to form an insoluble salt. The power to undergo coagulation is not abolished even in the case of oxalate blood, it is only suspended, for coagulation makes its appearance in an apparently normal manner if to the fluid oxalate blood a small quantity of some solution of a calcium salt be added.

The coagulability of blood may in some animals be diminished by intra-vascular injection of commercial peptone or of leech extract. Cobra poison also, as we have just seen, sometimes retards coagulation. Intravascular injection of commercial peptone—which really consists almost entirely of albumoses—retards coagulation of the blood in the dog, but not in the rabbit, and even in the case of the dog, coagulation is at times, for some as yet unexplained reason, unmodified.

As to the method whereby the commercial peptone acts it is impossible to dogmatise. For a time it was held that it forms an insoluble compound with the calcium of the blood, but this explanation was soon found to be inadequate. Contejean believes that the retarding influence on coagulation is indirectly brought about by a ferment elaborated in the liver, and that the formation of the ferment is under the influence of the hepatic nerves, for he found that when the cœliac ganglion is removed, intra-venous injection of peptone solution has no effect upon coagulation of the blood. Delezenne found that if a solution of peptone be passed through the liver of a dog which has only just been killed, a liquid is obtained able to suspend coagulation of blood *in vitro* and capable of rendering rabbit's blood incoagulable; these results are not produced by peptone solution *per se*. The liver seems to be the sole organ capable of producing the substance under the influence of peptone, for passage of peptone solution through intestine, spleen, kidney, lung, brain, or muscle were without effect. The results of Contejean and Delezenne have been confirmed by Gley and Pachon. According to W.

H. Thompson the effect of intra-venous injection of peptone differs according to the amount of the substance which is introduced into the circulation; if less than ·02 gm. per kilogram of body weight is added, coagulation of the blood is hastened, but if more than that amount is added coagulation is retarded. A similar peculiarity with regard to their action upon coagulation has been noted by Horne in the case of salts of the alkaline earths. He found that, though coagulation does not take place in the absence of a soluble compound of one of these elements, and though the addition of a small quantity hastens coagulation, the addition of a greater amount than ·5 per cent. retards the onset of coagulation.

To the three factors which have been mentioned above, Dastre and Floresco—in the case, at least, of peptone plasma—have lately added a fourth, viz., the reaction of the fluid. They find that fluids which have been rendered non-coagulable by the action of peptone are alkaline, and that the non-coagulability disappears if the fluids are neutralised or rendered faintly acid. In accordance with this observation is the fact that venous blood coagulates more rapidly than arterial blood.[1]

(ii.) **Pathological Increase of Coagulability. Thrombosis.**—We have already considered this subject so far as concerns the influence of the vessel wall upon thrombosis and the circulatory changes which are induced by the presence of a thrombus in a blood-vessel. We must now consider the formation of a thrombus somewhat more closely and from the point of view of the blood itself.

According to the difference of opinion as to whether the fibrin ferment is formed from blood-platelets, or is formed from the colourless cells of the blood, so the first step in the formation of a thrombus in a blood-vessel is differently described by different authors. According to Hayem, Bizzozero, and Eberth and Schimmelbusch, the blood-platelets play the principal part in the process; according to Zahn, Cohnheim and others, the leucocytes are the all-important elements. Eberth and Schimmelbusch maintain that thrombosis only occurs when the blood-stream is so far slackened that the blood-platelets, which normally travel in the axial stream, are no longer confined to it, but come into contact with the vessel wall. They regard injury of endothelium alone, therefore, as not being a sufficient cause for thrombosis; to it must be added slackening of the blood-flow. On the other hand, mere standstill of the blood is not sufficient to cause coagulation, for Baumgarten showed long ago that if a blood-vessel be ligatured in two places, and care be taken not to divide the intima, to disturb the vasa vasorum as little as possible, and to carry out the whole operation with strict asepsis, the included column of blood may remain fluid for weeks or months.

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[1] This statement is denied by some authors.

According to Eberth and Schimmelbusch, then, the first step in the formation of a thrombus is the collection of a number of blood-platelets at some point on the vessel wall; these by their disintegration give rise to fibrin ferment, and fibrin is deposited along with more blood-platelets upon the primary mass. Thenceforward the increase in size of the thrombus is easy. They allow that the agglomeration of leucocytes, which, according to Zahn, is the first step in the process, is to be seen, for example, when inflamed mesenteric capillaries and venules are examined under the microscope, but they maintain that these agglomerations are only temporary, and, therefore, cannot be the cause of thrombus formation.

J. Arnold, finding that particles of wheat meal injected into the jugular vein very soon become surrounded by leucocytes, has suggested that perhaps spontaneous thrombosis may be brought about by a somewhat different process to that which leads to thrombosis around an embolism, and, therefore, that both Eberth and Schimmelbusch and Zahn may be right.

*Appearance of a Thrombus.*—The macroscopic appearance of a thrombus is greatly modified by the rapidity or the slowness with which it is laid down. If a thrombus be laid down slowly (in a vessel, therefore, through which the blood is passing with some considerable degree of velocity, as, for example, on the wall of a saccular aneurysm), it is of a greyish-white colour, and has a well-marked laminated appearance on section; if it is laid down more rapidly, amongst the strands of fibrin are entangled varying numbers of red blood-corpuscles, which lend to the mass a greyish-red or brown appearance; while if it be laid down within quite a short time from blood which is scarcely moving, it is red. Thrombi are, therefore, spoken of as "white," "red," and "mixed." A true thrombus, or, as it is sometimes called, an "ante-mortem clot," being deposited from blood which is still in motion, has a very different appearance from a post-mortem clot; the latter is moister than a thrombus, is never adherent to the vessel wall, and never laminated, though it may show a division into a pale and a dark portion, from the fact that coagulation has not taken place until the specifically heavier red blood-corpuscles for the most part have sunk. It is true that at times there is a difficulty in distinguishing simple blood-clot from red thrombus, but these are cases in which the thrombus has been formed during the last hours of life, and even then, on examining into the relation which the coagulum bears to the vessel wall, the difficulty usually disappears.

*Fate of Thrombi.*—The ultimate fate which a thrombus undergoes depends entirely upon whether it is septic or aseptic. If septic, it must infallibly undergo disintegration, but if aseptic, it may either become organised, that is, replaced by vascularised fibrous tissue, or it may become the seat of calcification or of simple central softening. None of these terminations call for prolonged consideration here. Organisation may be left for the present, since it will be discussed along with the subject of repair; and disintegration of a septic thrombus may be passed over since it offers no differences from the softening of tissue that accompanies the formation of an abscess. Concerning calcification of thrombi, it is only necessary to state that it leads to the formation of concretions which are known as "phleboliths" or "vein-stones." Phleboliths are most commonly met with in the inferior hæmorrhoidal veins, when those veins have become varicose and led to the formation of hæmorrhoids or "piles." As in other situations in the body, so here the varicosity is a predisposing cause of thrombosis. Simple softening of thrombi is more commonly seen in the large globular thrombi of the heart than in any other region. It commences in the centre of the thrombus and gradually proceeds towards the periphery, converting the solid fibrin into a more or less viscid material of creamy consistency, the colour of which is yellow if the thrombus was originally white, or a more or less reddish-brown if the thrombus was originally mixed. The process is essentially a chronic one, and at times the amount of softened material is so great, and the wall formed by the unaltered thrombus is so thin, that the sensation known as "fluctuation" may be observed.

It is hardly necessary to repeat that, whether a thrombus be septic or aseptic, portions may be broken and carried to distant parts as emboli.

Besides the local formation of thrombi, the blood generally may show a greater tendency than normal towards coagulation. Experimentally, this condition may be induced in many ways. Thus, extensive and fatal intra-vascular clotting of the blood takes place after intra-vascular injection of a solution of nucleo-proteid. In human pathology little is known on the subject, but the blood taken from an inflamed area shows an increased tendency to coagulate. This very probably is due to the fact, that along with the blood is mixed a certain amount of inflammatory exudation which contains large numbers of leucocytes or the products of their destruction. From experiments upon animals it is my impression that the blood increases in coagulability as its specific gravity rises.

*Pathological Diminution of Coagulability.*—Many pathological conditions are known under which the coagulability of the blood is diminished. Such are the constitutional disease known as hæmophilia and conditions in which some toxic body is circulating in the blood. Thus, after death from asphyxia or poisoning by carbonic oxide gas or by hydrocyanic acid, or from septicæmia or the bite of venomous serpents, the blood in the heart and veins may be found fluid for as long as twenty-four hours. The blood change in septicæmia and after bites from venomous serpents is of particular interest, because the fact that snake venom contains albumose and that so many of the toxic bodies elaborated by micro-organisms are albumoses, brings the retardation of coagulation in these cases close to the retardation which is induced by intra-vascular injection of commercial peptone; whatever it may be, the cause of the retardation in both cases is probably the same.

It has frequently been suggested that the bleeding in hæmophilia is due to diminished coagulability of the blood. Judging from the fact that in some cases of hæmophilia, hæmorrhage can be arrested by the local application of a solution of calcium chloride, and that recurrence of hæmorrhage can be prevented by internal administration of calcium, it seems probable that an insufficient supply of this substance in the blood is sometimes the ultimate cause of the characteristic bleeding. Much work has been done on this point by A. E. Wright. But in other cases neither local nor internal administration of calcium produces the slightest effect, and one therefore looks towards the organic factors of coagulation for an explanation, and among them in particular to the colourless cells of the blood and the blood-platelets. So far, however, no satisfactory explanation of the "bleeding habit" has been given in this direction, and indeed the fact that profuse hæmorrhages sometimes occur as the result of trivial blows suggests that it may not be the blood which is at fault but rather the blood-vessels. Histological changes have been described in the small blood-vessels (Kidd), and, according to von Limbeck, the cause is to be sought in some toxic substance, at present unknown, which alters the constitution of the finest branches of the vessels in such a way that they rupture either spontaneously or from slight causes.

**II. The Specialised Elements of the Blood.—(i.) The Red Cells of the Blood.**—(*a*) *Varieties present in Blood.*—Variations of red blood-corpuscles within physiological limits are relatively few. It is known that the red corpuscles are not of uniform size, and Hayem distinguished in the blood of adults (1) small or dwarf corpuscles which have a diameter of 6–6·6 $\mu$, and form about 12 per cent. of the red cells, (2) medium-sized corpuscles which have a diameter of 7·5 $\mu$ and form about 75 per cent. of the red cells, and (3) large or giant corpuscles which have a diameter of 8–9 $\mu$ and form about 12 per cent. of the red cells. In addition to these, there is in normal blood a small number of irregular cells which, from their small size (usually 2·5–3 $\mu$), are known as microcytes. Under pathological conditions, the number of microcytes is apt to increase considerably; it is probable that they are merely disintegration products of red blood-corpuscles. In infancy, besides the above-mentioned varieties, giant corpuscles (megalocytes) are also to be found with a diameter of 10 $\mu$ or more.

A distinctly pathological condition is that in which poikilocytes are present. Poikilocytes are degenerated forms of red blood-corpuscle in which the normal discoidal outline of the corpuscle gives place to an irregular spinous appearance. The corpuscles are shrunken, they have to a large extent lost their normal tendency to form rouleaux when the blood is shed, but they frequently remain more or less bi-concave.

Another form of degeneration to which red blood-corpuscles are liable is that which has been studied especially by Maragliano. It consists in death or necrobiosis of the cell, whereby it loses that elective receptivity for certain stains (*e.g.*, eosin) which characterises normal blood-corpuscles when a film of dried blood on a cover-slip is exposed to a mixture of stains (*e.g.*, eosin and methylene blue). This necrobiosis takes place first in the centre of the cell and shows itself either by an irregular or diffuse staining, or else by a disappearance of the colouring matter of the blood in this situation, and the appearance on staining of a colourless centre surrounded by a broader or narrower triangular, circular, or elliptical outline of stained material. The necrobiotic process is accompanied, according to Maragliano, by active amœboid movements of the peripheral portions of the cell, which thrusts out pseudopodia; the corpuscle ultimately comes to form a poikilocyte. Both poikilocytosis and necrobiotic degeneration are most commonly met with in cases of severe anæmia and in conditions in which the blood-plasma has been altered by the addition to it of different kinds of toxic material, such as chloroform, weak acids and alkalies.

Besides the normal and degenerated forms of red blood-corpuscles, in all cases of anæmia there is to be found a greater or smaller number of nucleated red blood-corpuscles. Ehrlich divides these into normoblasts and megaloblasts or gigantoblasts. Normoblasts are nucleated red blood-corpuscles of the size of a normal red blood-corpuscle; the nucleus stains readily with basic dyes such as methylene blue, and the cell body with acid dyes such as eosin. As a rule, the nucleus is single, but occasionally more than one is present, or the single nucleus may be multipartite. Megaloblasts are twice to four times the size of normoblasts, contain much hæmoglobin, and differ (according to Ehrlich) from normoblasts in that their nuclei are not extruded from the cell to form red blood-corpuscles, as he believes is the case with normoblasts, but degenerate within the cell and are finally broken up. On the breaking up of the nucleus the megaloblast becomes converted into a megalocyte.

(*b*) *Numbers present in Blood.*—Speaking broadly, it may be said that the blood of a healthy adult man contains 5,000,000 red blood-corpuscles per cubic millimetre, and that the blood of a healthy adult woman contains 4,500,000 red blood-corpuscles per cubic millimetre. These figures, however, are only approximate, for the estimations of different authorities vary between such wide limits as 3,000,000 and 7,000,000 per cubic millimetre; nevertheless, 3,000,000 would be by most authors regarded as clear evidence of oligocythæmia and 7,000,000 as equally clear evidence of polycythæmia.

Oligocythæmia naturally comes to be classed amongst the anæmias and it will not be considered here, though it must be noted that abstinence from food, even if short of starvation, reduces the number of red blood-cells to a certain extent.

Polycythæmia is best seen in the case of new-born infants. Schiff gives a table which shows that the number of red blood-corpuscles in a certain case during the first five days of life was above 6,000,000 per cubic millimetre. The number on the second day of life was nearly 8,500,000, but it rapidly decreased and reached the normal on the sixth day. A relative degree of polycythæmia, of course, exists in every case in which the volume of the blood-plasma is diminished from whatever cause, without a corresponding diminution in the number of red blood-corpuscles; it is therefore probable that part, at all events, of the polycythæmia of the new-born depends upon the loss of fluid which the child suffers upon the establishment of respiration, a loss which is not counterbalanced during these early days of life by a corresponding intake.

The number of red blood-corpuscles also varies according to the nutrition of the individual, the season of the year, the altitude at which the individual lives, the climate, tropical or temperate, and (in the case of women) during pregnancy, lactation and at the climacteric. But of these physiological variations it is unnecessary to speak, especially in view of the fact that upon the whole subject there are practically but three points upon which authorities are fully agreed, and these are: 1, that polycythæmia occurs in new-born infants; 2, that polycythæmia occurs when nutritive conditions are extremely good; and 3, that oligocythæmia occurs when the nutrition is insufficient.

(ii.) **The Colourless Corpuscles of the Blood.** — (*a*) *Varieties present in Blood.*—That the colourless corpuscles (wandering cells, leucocytes) of the blood are not all of one kind was recognised by Wharton Jones in 1846. He divided them into granular and nucleated cells, while he recognised further that some of the granules are fine, others coarse. Max Schultze in 1865 examined the living cells on the warm stage and described (*a*) small round cells with large nucleus and no amœboid movements; (*b*) cells larger than (*a*) with more protoplasm and showing amœboid movement; (*c*) mono- or poly-nucleated cells with fine granules, showing amœboid movement, these being the commonest of all the colourless blood-cells; (*d*) amœboid cells with large numbers of coarse granules. In 1878 and the succeeding years Ehrlich revolutionised the study of colourless cells by showing that the granules react in different ways to staining reagents. He had already found that in staining by various dyes—principally derivatives of anilin—the staining property is, in some cases, associated with the acid portion of the compound, sometimes with the basic portion, and sometimes with the neutral "salt" that is formed by the combination of the acid and base. He therefore divided stains into acid (*e.g.*, eosin), basic (*e.g.*, methylene blue), and neutral (*e.g.*, formed in a mixture of methylene blue and "acid fuchsin"). He distinguished the granule-bearing colourless cells according as their granules stained with one or other of these dyes when they were exposed to a mixture of all three. He described five forms of granulation, which, in the case of the blood, gave the following classes:—

(1) *Cells with granulation* $\alpha$.—The granules are large and stain brilliantly with eosin. These cells he therefore called shortly "eosinophil" cells.

(2) *Cells with granulation* $\beta$.—The granules are fine and stain both with acid and basic dyes in a mixture of both. The cells are therefore termed "amphophil"; these cells Ehrlich found in the rabbit.

(3) *Cells with granulation* $\gamma$.—The granules are large but not so large as in granulation $\alpha$, they stain with basic dyes, and the cells are therefore "basophil" with coarse granules. These cells are represented principally by the "Mastzellen," large cells found in connective tissue in most vertebrates, but represented in human blood only in certain cases of leuchæmia.

(4) *Cells with granulation* $\delta$.—Mononuclear cells, the granules of which stain with basic dyes and are small.

(5) *Cells with granulation* $\epsilon$.—Polynuclear cells, the granules of which are "neutrophil," staining neither with acid nor with basic dyes. These cells are the most common of all hæmal leucocytes.

Kanthack and Hardy, working principally with the frog and rat, have found that the colourless cells of the body differ according as their normal situation is the blood or the body cavity, with which is included the connective tissue spaces. Speaking generally, the former or hæmal wandering cells are characterised by their smaller size and the smaller size of their granules, the latter or cœlomic wandering cells are characterised by their larger size and the larger size of their granules. They found that Ehrlich's "neutral" dye is not neutral but really faintly acid, and that the neutrophil and amphophil granulations are really faintly acidophil or oxyphil. They therefore simplify the classification of the wandering cells of the body by arranging them in the following way[1]:—

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[1] This classification is adopted in this work.

- I. Oxyphil cells
  - Finely granular.
  - Coarsely granular.
- II. Basophil cells
  - Finely granular.
  - Coarsely granular.
- III. Hyaline cells.
- IV. Lymphocytes.

Metchnikoff, from the phenomenon which is commonly observed among the wandering cells of the body of englobing foreign particles of various kinds, has named certain of them "phagocytes," and he distinguishes two varieties, "macrophages" and "microphages." The former are to be met with in a variety of situations, and especially in the liver; their general appearance is that of a hyaline or an endothelioid cell. The microphages are the finely granular oxyphil (neutrophil) cells of the blood.

Adami, in his article on "Inflammation" in Allbutt's *System of Medicine*, has drawn up a very useful table, in which are collated the different classifications of the varieties of leucocyte or wandering cell. It is reproduced below.

*Collation of the different classifications of the varieties of leucocytes (Adami).*

| Kanthack and Hardy. | Ehrlich. | Metchnikoff. | Max Schultze. | Wharton Jones. |
|---|---|---|---|---|
| Lymphocyte, . | Lymphocyte, . | Lymphocyte. | Small round cell I. | Non-granular nucleated cells. |
| Hyaline cell, . | ... | Macrophage. | Large round cell II. | |
| Coarsely granular oxyphil cells, | Eosinophil cell. . | Eosinophil cell. | Cells with coarsely granular protoplasm. | Granule cells, coarsely granular. |
| Finely granular oxyphil cells, . | Neutrophil<br>Amphophil cells, | Microphage. | Cells with finely granular protoplasm. | Granule cells, finely granular. |
| Coarsely granular basophil cells, | Basophil cells with $\gamma$ - granulation. Mastzellen, | ... | ... | ... |
| Finely granular basophil cells, | Basophil cells with $\delta$-granulation, | ... | Cells with finely granular protoplasm. | ? Granule cells, finely granular. |

Von Limbeck divides the wandering cells of the body from the clinico-pathological standpoint somewhat differently. He makes five divisions:—

(1) Eosinophil cells, the nucleus of which is polymorphous; this group contains some of Ehrlich's amphophil cells.

(2) Neutrophil cells, which include the greater number of all

wandering cells of the blood (70–80 per cent. both in normal and pathological conditions) and also includes the greater number of lymphocytes.

(3) Basophil cells: small cells of about the size of a red blood-corpuscle, having a round nucleus and coarse granules which are smaller than eosinophil granules. It is doubtful whether they are present in the blood of man during health or any disease but leuchæmia, and even in leuchæmia they are rare.

(4) Mastzellen.

(5) Medullary cells (Markzellen): very large cells, the nuclei of which are poor in chromatin and, therefore, do not stain deeply, and are generally of sufficient size to occupy the greater portion of the cell. These cells arise from bone-marrow and some of them are eosinophil.

(*b*) *Numbers present under Physiological Conditions.*—Subject to the reservations made below, the number of leucocytes in normal blood may be said to be about 10,000 per cubic millimetre. In human blood the hyaline cells and lymphocytes constitute about 20–30 per cent. of the total number of leucocytes, the finely granular oxyphil cells constitute 50–70 per cent., and the coarsely granular oxyphil cells constitute 1–5 per cent. It is impossible to give more definite proportions than the above, as the variations are very great, but it may roughly be said that in human physiological blood the vast bulk of leucocytes consists of finely granular oxyphil cells and lymphocytes, and that if the proportion of the former be low, there is generally a greater proportion than normal of lymphocytes.

Physiological variations in the numbers of leucocytes are even more common than physiological variations in the number of red blood-corpuscles. Increase in the number of leucocytes is spoken of under the general name of "leucocytosis," and there is a physiological and a pathological leucocytosis as well as one brought about by the action of certain drugs. A physiological leucocytosis occurs in digestion, when the number of leucocytes in the blood is frequently doubled; here the increase is principally due to the number of lymphocytes which are washed into the blood from the lymphatic glands by the lymph and chyle, the amount of which and the rapidity of flow of which are increased during digestion. In starvation the number of leucocytes in the blood diminishes ("leucopenia"). Thus, in the case of the fasting man Succi, it was found that the number of leucocytes in his blood fell during the first week of his fast from 14,530 per cubic millimetre to 861 per cubic millimetre. In the new-born a leucocytosis constantly occurs; it is comparable to the polycythæmia which we have already described, and probably owns somewhat the same explanation. In pregnancy a leucocytosis, though common, is not invariable. Pathological leucocytosis and leucopenia will be considered later.

(iii.) **The Blood-Platelets.**—(*a*) *Characters.*—Blood-platelets were first described under that name by Bizzozero in 1882, but they are the same elements as Hayem described in 1877 under the name of "hæmatoblasts" from the function which he ascribed to them. There is no doubt, however, that they had been recognised though not fully investigated by previous observers. They are small circular or ovoid bodies having a diameter of 3–3·5 $\mu$, and a dull, finely granular appearance; they are destitute of hæmoglobin, stain faintly with anilin dyes, and are very easily destroyed. Their instability in the presence of mechanical, chemical, and thermal agents, and their tendency to club together and to attach themselves to red blood-corpuscles and leucocytes in diluted and in undiluted blood are their principal characteristics. By Löwit they are regarded in part as artificial products formed from globulin separated from the blood-plasma, in part as destruction products of the colourless blood-corpuscles, but it has been shown by Laker and Bizzozero that they can be seen circulating in the blood-vessels of the bat's wing. It is therefore generally accepted that blood-platelets are separate and distinct elements of the normal blood. Lilienfeld, however, maintains that the micro-chemical reactions of blood-platelets are identical with those of the nuclei of leucocytes, and he therefore regards blood-platelets as being derived from the nuclei of leucocytes.

(*b*) *Numbers.*—The number of blood-platelets in normal blood has been variously estimated from 180,000 to 500,000 per cubic millimetre. Physiological variations in the numbers of blood-platelets have hardly been investigated. In pathological conditions, apart from the rôle which they may play in thrombosis (and this we have already sufficiently discussed), it has been found by Afanassiew and Fusari, and confirmed by von Limbeck, that in afebrile anæmias, especially when there are signs of regeneration in the blood, the blood-platelets are increased in number. They have thus been found in larger numbers than normal after hæmorrhage (Hayem), and in leuchæmia (Afanassiew and Pruss). After poisoning with various blood-poisons (*e.g.*, pyrogallic acid, glycerine, iodine solution) they diminish in number. With consistently high fever (*e.g.*, typhoid fever and erysipelas, but not in tuberculosis or pneumonia) their number is, as a rule, diminished. Pizzini says that they are diminished in numbers in all febrile conditions, and that their diminution runs parallel with the height of the fever and the rapidity with which the temperature rises. In malaria, blood-platelets sometimes vanish completely from the blood, but they increase in number after the fall of temperature has taken place and reach their maximum 6–7 hours after the crisis.

III. **The Anæmias.**—We now come to discuss the clinical condition known as anæmia. Essentially, this condition is one in which the blood is present in insufficient quantity, and as the clinical recognition of the existence of a sufficient amount of blood in the body was based (before use of the microscope became general in medicine) upon the presence of a healthy pink colour of the skin and a full redness of the mucous membranes, so anæmia was clinically recognised by a pallor in the same regions. Of course anæmia and pallor go together in the greater number of cases, but it is now known that a considerable degree of anæmia may exist and yet the colour of the patient may not be far removed from the normal.

Pallor, quite apart from the pallor due to constriction of small blood-vessels,—and with this condition anæmia in our present sense of the word has nothing to do,—must be due to a deficiency of hæmoglobin in the part. That deficiency, it is obvious, may depend (1) upon an absolute diminution in the number of red blood-corpuscles in the part, the hæmoglobin content of each red blood-corpuscle which is present being up to the standard; or (2) upon a relative poverty in the amount of hæmoglobin in each red blood-corpuscle, the numbers of red blood-corpuscles present being normal; or (3) upon a combination of the two preceding conditions, fewer red blood-corpuscles, each having a lower hæmoglobin content, being present in the part; or (4) upon a relative increase in the number of leucocytes in the blood, the number of red blood-corpuscles and the amount of hæmoglobin in each being normal; or (5) upon a relative increase in the number of the leucocytes, conjoined with either a diminution in number of the red blood-corpuscles or a diminution in the hæmoglobin content of each corpuscle, or with both of these latter conditions.

The anæmias have been divided in many ways. The most common is that by which "primary" or "essential" anæmia is divided from "secondary" anæmia; but apart from the great difficulty that an anæmia which is at the present time regarded as primary may ultimately come to be considered as secondary, there is the overwhelming objection to this mode of division that it unites under one heading varieties of anæmia that are pathologically distinct. A simple, as well as a fairly satisfactory, basis for division can be found in the microscopical appearance of the blood in different cases. In some cases, the point which arrests attention is that the number of leucocytes seen in any field of the microscope is greatly increased, in others this increase in the number of leucocytes is not noticed. No doubt there are numerous gradations between these two extremes, but since the difference on this point is usually well-marked, and since it corresponds to other marked pathological differences, it is convenient to take this definite fact as the basis of our division, and to consider the anæmias according as this most striking change of the blood is present or absent. We shall therefore divide the anæmias into two great classes as follows:—

*Group I.*—Anæmias in which marked changes in the numbers or characters of the white blood-corpuscles are *absent.*

*Group II.*—Anæmias in which marked changes in the numbers or characters of the white blood-corpuscles are *present.*

It is necessary to look closely into the kind of case that each of these groups represents. With regard to the first, it is clear that the leucocytes may be left out of consideration entirely, and it might be thought that it would be simpler to describe the group as anæmias depending upon changes in the red blood-corpuscles. But a closer examination of the anæmias included under Group II. shows that such a definition for the anæmias of Group I. would be unsatisfactory, since it is obvious that nothing whatever is said or even implied concerning the red blood-corpuscles by the definition that has been given for the anæmias of Group II. And, as a matter of fact, though in anæmias of Group II. the leucocytic changes are so marked as almost to detract attention from the changes in the red blood-corpuscles, yet it is found, when special attention is paid to the point, that in a very large number of cases belonging to this group, the erythrocytic changes are as extreme as in many of the anæmias of Group I. However, there is no doubt that, in discussing the anæmias of Group I., it will be necessary to consider, above all, the red blood-corpuscles, and that, when discussing the anæmias of Group II., the white blood-corpuscles will chiefly call for attention ; but it must be remembered that the changes in red blood-corpuscles will be dismissed summarily in the latter case, not because they are ill-marked or unimportant, but because they are identical with those changes which will have been discussed fully along with the anæmias of Group I. All forms of anæmia of any severity, without exception, are accompanied by erythrocytic changes, but in some leucocytic changes are unimportant, in others they are highly important.

(i.) *Group I.*—**Anæmias in which marked Changes in the Numbers or Characters of the White Blood-Corpuscles are Absent.**—Since the anæmias of Group I. essentially depend upon changes in the red blood-corpuscles, they may be regarded from two points of view: either from that of the number of red blood-corpuscles present, or from that of the hæmoglobin content of the red blood-corpuscles themselves. It is obvious that either of these conditions might exist independently of the other. Thus the anæmia found during the first few hours[1] after a sudden profuse hæmorrhage has taken place, is due solely to a diminution in the number of red blood-corpuscles present in each cubic millimetre of blood; the amount of hæmoglobin in each corpuscle that remains is up to the normal standard. But the anæmia of young women, which is known as "chlorosis," frequently depends simply upon a diminution in the amount of hæmogoblin contained in each red blood-corpuscle, the number of corpuscles being normal.

It would be very convenient if such a distinction could be used to sharply subdivide the anæmias of Group I., but unfortunately for our purpose this is only possible to a limited extent. In many cases where the number of red blood-corpuscles is diminished to any considerable extent, the hæmoglobin content of each corpuscle sooner or later becomes lowered also,—not only is oligocythæmia present, but oligochromæmia is present also. One cannot even place the conditions of the blood which are brought about by hæmorrhage in a class by themselves in this respect, for the question of the presence or the absence of oligochromæmia largely depends upon the manner in which hæmorrhage has taken place and the length of time that elapses between the cessation of hæmorrhage and the examination of the blood. Nevertheless it is necessary to divide the subject in some way for purposes of description, and after the cautions that have been given it is not likely to cause misconception if we subdivide Group I. into (A) Anæmias in which the principal change is a diminution in the number of red blood-corpuscles, and (B) Anæmias in which the principal change is a diminution in the hæmoglobin content of the individual red blood-corpuscles.

A. **The Principal Change is a Diminution in the Number of the Red Blood-Corpuscles.**—When hæmorrhage leads to anæmia it is of necessity either profuse or long-continued. Among the profuse hæmorrhages those in which the blood comes from an artery are the most important. The artery may be opened by an injury such as a stab or cut, or may be opened by an ulcerative process; of the latter kind are the hæmorrhage which occurs in the rupture of an aneurysm, the hæmorrhage into the stomach occurring in chronic gastric ulcer (hæmatemesis), the hæmorrhage into the intestines sometimes seen in the later stages of typhoid fever and leading to melæna, the hæmorrhage which occurs during the necrosis of a malignant growth, etc. In such cases the loss of blood may be so great as to be fatal within a few minutes, but it may be arrested by natural or by surgical means after producing a more or less severe degree of anæmia. Of course it is immaterial in this respect whether the bleeding be external, as in the case of hæmorrhage from the carotid in a case of cut throat, or internal, as in the case of rupture of an abdominal aneurysm. A large amount of blood may also be lost when the bleeding does not take place from an artery as in the examples given above. Cases of this kind are to be seen in hæmorrhage from congested tissues; such are some forms of hæmatemesis occurring in cirrhosis of the liver, hæmorrhage from rupture of a varicose vein, hæmorrhage from rupture of a tubal gestation. In other cases anæmia is produced, not so much because the hæmorrhage is profuse, as because it continues for a considerable length of time; thus the oozing of blood from capillaries in hæmophilia and in menorrhagia and metrorrhagia (in which the blood comes from a congested uterine mucous membrane in quantities that are not excessive in themselves, but in which the loss of blood extends over weeks and months) are of this kind. So, too, is the anæmia which results from the presence of certain entozoa[1] in the intestine. All these forms of hæmorrhage may produce the most extreme blanching, and in all the essential condition of the blood is the same. It consists in an absolute diminution in the number of red blood-corpuscles, an absolute increase in the amount of blood-plasma, a lowering of the specific gravity of the blood and of the blood-plasma. Thus, instead of five million red blood-corpuscles per cubic millimetre of blood, three, two, one, or even less than one million, may be present; the blood-plasma may have a specific gravity of 1021 instead of about 1026; and the specific gravity of the blood may be 1035 instead of 1058.

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[1] Sherrington and Copeman found in the rabbit that the number of red corpuscles in blood is not at its minimum until 15–25 minutes after cessation of hæmorrhage. Bizzozero and Salvioli (cited by these authors) found that the minimum does not occur till 24–48 hours have elapsed. My own observations on œdema, etc., indirectly, but strongly, support Sherrington and Copeman.

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[1] The entozoon of chief importance in this connection is *Anchylostomum duodenale*, a nematode worm 6–10 mm. in length, which has a head provided with two strong jaws. By these it attaches itself to the mucous membrane of the duodenum, jejunum or ileum, and lives on the blood of its host, which it sucks therefrom. After awhile it drops off, but bleeding continues from the small incision which it has made. It is the subsequent hæmorrhage which takes place into the bowel from these lesions, and not the amount of blood which the parasite itself abstracts, that is the essential cause of the ultimate anæmia which results. The number of parasites present in the host is very variable; numbers from 24

Immediately after a profuse hæmorrhage has taken place the hæmoglobin content of the individual corpuscle is normal, but after a short lapse of time, and at all times during the existence of anæmia due to protracted small hæmorrhages, it is found that the hæmoglobin content of the blood is diminished. The following marked examples of this condition are given by Zappert[1] in the case of anæmia due to the presence of *Anchylostomum duodenale* in the intestine.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (1) | 4,350,000 | red blood-corpuscles | per cubic | mm. with | 50 | p.c. hæmoglobin | present. |
| (2) | 2,490,000 | ,, | ,, | ,, | 25 | ,, | ,, |
| (3) | 4,384,000 | ,, | ,, | ,, | 40 | ,, | ,, |
| (4) | 3,204,000 | ,, | ,, | ,, | 40 | ,, | ,, |
| (5) | 4,272,000 | ,, | ,, | ,, | 30 | ,, | ,, |

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to 500 have been counted after the death of the patient. This form of anæmia is common in Egypt and Brazil, but sporadic cases or even small epidemics have been recorded in various parts of Europe, especially in Italy and Switzerland. One of the best known of these epidemics occurred among the Italian labourers during the building of the St Gothard tunnel. It is difficult to understand how the anæmia can be so profound as it undoubtedly is in these cases, if one is restricted to the belief that the action of the parasite is confined to the formation of a small puncture in the mucous membrane. One would reasonably expect that the amount of blood lost by subsequent hæmorrhage into the intestine even from 500 punctures in the mucous membrane would be comparatively small, though no doubt it must be remembered that fresh punctures are constantly being made. Bearing in mind the effect of injecting leech-extract into the circulation of an animal, it is at all events conceivable that the anchylostomum not only withdraws blood from its host but also injects into him some substance which diminishes the coagulability of his blood. Under those conditions a state akin to that which probably obtains in some cases of hæmophilia would be present and the greatness of the hæmorrhage, combined with the smallness of the lesion, would be explicable. Other entozoal causes of anæmia, such as *Bothryocephalus latus* and *Anguillula intestinalis*, do not call for special remark here.

[1] Cited by von Limbeck, *Path. d. Blutes.*

If the case does not end fatally, within a very short time the appearance of normoblasts and megaloblasts in the blood gives evidence of a commencing regeneration of red blood-corpuscles; megaloblasts are less commonly seen than normoblasts, and according to Ehrlich their presence is an indication that the regenerative process is not proceeding upon absolutely normal lines. As the number of red blood-corpuscles increases and the anæmia disappears, so the normoblasts diminish in numbers. In some cases the nucleated red blood-corpuscles seem to be ejected into the blood periodically. Poikilocytosis is also observed but far less commonly than under certain other anæmic conditions. According to von Limbeck (*loc. cit.*, p. 345), the leucocytes in hæmophilia undergo a slight and transitory increase in numbers, and, as will be seen later, after a considerable amount of blood has been lost, from whatever cause, there is a leucocytosis lasting for two or three days. As in most of the other forms of anæmia, the number of blood-platelets is increased.

The anæmias that have been mentioned above, all depend upon conditions in which blood is completely lost to the body by the opening of a blood-vessel, whether artery, vein or capillary, and in such cases the red blood-corpuscles are lost as such. But in certain other conditions there occurs a definite destruction of blood-corpuscles within the blood-vessels themselves. The best example of this class of case is seen in malaria, but it also occurs when certain toxic substances, such as bile acids, toluylene-diamin, etc., are circulating in the blood. There is also reason to believe that blood destruction occurs in the so-called progressive pernicious anæmia.

In malaria the red blood-corpuscles are actually destroyed by animal parasites[1] and the process of destruction can be followed microscopically in all its stages. During the growth of the parasite within the red blood-corpuscle, the hæmoglobin is converted into an iron-free pigment known as melanin, and the

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[1] The protozoa of malaria are generally, but not universally, regarded at the present day as being of several kinds. Of these the most important are: (1) the parasite of typical quartan ague, (2) that of typical tertian ague, (3) that of æstivo-autumnal fever. These parasites present differences amongst themselves into which it is impossible to enter here, but the principal difference, and that upon which the length of the afebrile state of the patient depends—for it is immediately before the rise of temperature which ushers in the ague fit takes place, that the parasites are recognised in greatest numbers in the blood—has reference to the length of time which the parasite requires for the completion of the cycle of its life history.

After overcoming a considerable amount of opposition, the three types under which Laveran described the parasite as occurring, are now generally recognised. He distinguished spherical bodies (plasmodia), crescentic bodies, and flagellate bodies. The relation of these forms to one another is now fairly well established, and it is known that they correspond with different stages in the life history of the same parasite. There is little doubt, however, that Laveran's original view, that only one variety of malaria parasite exists, is incorrect. The spherical bodies are the most numerous of all forms met with in the blood. They are young forms of the parasite, have a diameter varying between 1 μ and 7 μ, and multiply by sporulation, the spores frequently being arranged in a ring and producing the "rosette" form described by Golgi. The smallest and youngest spherules have a hyaline protoplasm, but the older parasites invariably contain granules of melanin. The protozoon inhabits a red blood-corpuscle, lives at the expense of its hæmoglobin, increases in size, multiplies by endogenous sporulation, and ultimately, by rupture of the blood-corpuscle and the protozoon, the individual sporules are set free. The parasite is therefore found under endoglobular and ectoglobular conditions. Crescentic forms are not met with in all cases of malaria. Their length is 8–9 μ and their greatest breadth 2 μ. They are found either free in the blood-plasma or adherent to red blood-corpuscles. They almost invariably show pigment granules in the middle third. Occasionally they develop into elliptical forms. Since crescentic bodies remain in the blood for days or weeks after spherules have disappeared either spontaneously or as the result of medicinal treatment, since they undergo no development in the red blood-corpuscles, and since they may become flagellate, Manson regards them as the form in which the life of the species is carried on outside the human body. Flagellate bodies are less commonly observed than either of the others, but Manson believes that they are to be found in all cases if certain precautions be taken. They are always ectoglobular, and on making a fresh microscopic preparation of the blood are not seen at first, but become visible about fifteen minutes after the blood has been shed. They are spherical and are provided with from one to four flagella, whose length frequently is 3–4 times the diameter of a red blood-corpuscle. By means of the lashing movements of the flagella, the organism swims freely in the blood-serum of the preparation. Either spherical or crescentic bodies may become converted into flagellate bodies. The parasite has never been cultivated outside the body, nor has it been found possible to convey the disease to other animals than man, by inoculating with blood from a patient who is suffering from malaria and whose blood contains one or other variety of the parasite. That it can carry on an existence outside the human body is certain, but whether that existence is active or resting, whether it is connected with earth, air, or water, or with other animals (*e.g.*, the mosquito, as Manson suggests), it is impossible at present to say. Judging from the fact that the regions in which malaria is endemic are marshy, it seems probable that water plays an important part in the life history of the parasite. But in spite of numerous attempts and positive assertions to the contrary, the protozoon has never been found except in the blood of patients suffering from the disease. Nevertheless, Ross, following up Manson's suggestion, has found the protozoa in the stomachs of mosquitoes engorged with the blood of malarial patients, and says that he has given malaria to healthy men by administering to them water in which malariated mosquitoes have died.

corpuscles themselves are broken up. The presence of melanin granules in the body of the parasite shows that it lives at the expense of the hæmoglobin. It follows, therefore, that a deficiency of red blood-corpuscles is produced, and long before the micro-organism of malaria was discovered by Laveran in 1880 it was recognised that malaria is one of the most important causes of anæmia. The diminution in number of the red blood-corpuscles may be so great that not more than 500,000 per cubic millimetre are present. Reduction to 2,500,000 is by no means uncommon. The destruction of corpuscles takes place essentially during the periodic "ague-fit," and the number that is destroyed depends upon the severity of the attack; it has been found (Dionisi and others) that a single ague-fit may lead to a destruction which varies between 200,000 and 1,000,000 corpuscles per cubic millimetre. As a rule, when the disease lasts some time, it is found that the hæmoglobin content of the corpuscles that are undestroyed after an attack is diminished also, and therefore in the later stages of malaria, oligochromæmia as well as oligæmia is present.

With regard to the leucocytes there is a general agreement that neither during malarial attacks nor in the intervals between them is there any increase in their numbers; in some cases, indeed, a diminution has been noted. On the other hand, Billings found that sometimes in the post-febrile stages of severe malaria a marked increase in the number of leucocytes occurs. Thus he mentions cases in which 30,000–40,000 were present per cubic millimetre. Such cases, however, are uncommon, but when they occur the leucocytes are found to contain large numbers of melanin granules. It has already been stated that during the height of a severe ague-fit, blood-platelets may completely disappear from the blood, and that they undergo a remarkable increase in numbers after the temperature of the patient has fallen.

*Toxic Anæmias.*—Anæmia, resulting from the direct action of some toxic substance, the nature of which is known, is of comparatively rare occurrence, unless the poison have been circulating in the blood for some considerable time. It occurs in chronic poisoning by lead and arsenic, but it is open to doubt whether these cases should be considered in the present connection. As the result of acute poisoning, however, by such substances as chlorate of potassium and arseniuretted hydrogen in man and animals, and acute poisoning by intra-vascular injection of a variety of substances, such as glycerine, toluylenediamin, bile acids, in experimental work upon animals, it is found that anæmia, as represented by the microscopical examination of the blood, may exist to an extreme degree. In all the examples given the red blood-corpuscles are affected; either they are directly broken up, or more commonly they lose their hæmoglobin, which then becomes dissolved in the blood-plasma. These acute poisonings are, therefore, accompanied by other symptoms than anæmia, the most important of which are hæmoglobinuria and jaundice. But besides hæmoglobin and bile-pigments, other products of the destruction of the colouring matter of the blood (*e.g.*, urobilin) may find their way into the urine, or may be deposited in some of the tissues. The fact that anæmia, in a very marked degree, is frequently seen in cases of acute infective disease, suggests that in these cases a blood destruction occurs analogous to that which can be produced by the intra-vascular injection of different toxic bodies into animals. Moreover, the possibility that this is the case is further supported by the fact that, in these same acute infective diseases, the amount of pigment present in the urine is commonly greater than normal.

The microscopical appearances of the blood in cases of acute toxic poisoning, of course, differs according to the action of the hæmolytic agent. If the hæmoglobin be dissolved from the red blood-corpuscles, but the corpuscles themselves be not broken up, we have a form of anæmia such as will be discussed later; but if the corpuscles be definitely broken up (toluylenediamin), the number of red blood-corpuscles is diminished, irregular forms are seen in the blood, and later, all the varieties of blood-cell met with in regeneration of blood are found. It is this latter variety of toxic action which is of especial importance in connection with anæmias in which the number of red blood-corpuscles is diminished; and it is of the greater interest, in that the disease known as progressive pernicious anæmia bears many resemblances to anæmia of this type. Though it is clear that toxic substances act in different ways upon the blood, the subject—though important—is one concerning which very little is known.

Progressive pernicious anæmia differs clinically from the varieties of anæmia that we have hitherto considered in that it apparently always proceeds to a fatal termination, that it is especially liable to affect males, and that it resists medicinal treatment, to which many other forms of anæmia are often readily amenable. In the blood of patients suffering from pernicious anæmia are to be found all those varieties of corpuscles that are found in other cases of severe anæmia; thus, along with an excessive diminution in the number of red blood-corpuscles, there is the presence of poikilocytes, microcytes, megalocytes, normoblasts, megaloblasts. The number of red blood-corpuscles present is usually very small; Quincke published in a case of this disease the smallest number—143,000—of red blood-corpuscles per cubic millimetre that I have found recorded. As in other cases of severe anæmia, in which the number of red blood-corpuscles is very greatly decreased, the hæmoglobin content of the corpuscles that remain may be up to the normal standard, indeed in some cases it is above the normal. It was thought at one time that this diminution in the number of red blood-corpuscles, with relative richness in hæmoglobin, constituted a characteristic feature of pernicious anæmia, but this is now known not to be the case. Pernicious anæmia is certainly associated with marked destruction of red blood-corpuscles. For, as Quincke and others have shown, there is a deposit of iron in the liver, spleen, kidneys, which can only be regarded as arising from the disintegration of hæmoglobin; moreover, the disease is not infrequently accompanied by the presence of slight degrees of jaundice, and an excessive amount of altered blood-pigment (especially urobilin) in the urine is a very constant feature. Ehrlich is inclined to regard the large number of megalocytes present in the blood as characteristic of pernicious anæmia. No change is to be noticed, as a rule, in the numbers or characters of the leucocytes, but the blood-platelets are frequently present in greatly increased numbers. The specific gravity of the blood is very considerably lower than normal. In five cases Lloyd Jones found that it lay between 1029 and 1040.

B. **Anæmias in which the Principal Change is a Diminution in the Hæmoglobin Content of the Red Blood-Corpuscles.**—The most important variety of anæmia that depends upon a diminution in the hæmoglobin content of the red blood-corpuscles is that which, from the peculiar greenish hue which it confers on the patient, is known as "chlorosis." This condition is most commonly met with in young women, and is probably to be regarded, as Lloyd Jones suggests, as an excessive manifestation of that fall in specific gravity of the blood which he has shown to be normal in women about the age of puberty. It is about the same period of life that chlorosis occurs, only the fall in specific gravity of the blood in chlorosis is much greater than normal. Not infrequently the specific gravity of the blood-plasma, or rather the blood-serum, is higher than normal, and this must probably be ascribed to a greater percentage composition of proteid.

In this, as in so many other forms of anæmia, oligocythæmia and oligochromæmia are often associated, but, as is shown by an average of fifty-five estimations in fifteen cases[1] made by various authors and collected in a table by von Limbeck (*loc. cit.*, pp. 305–6), the hæmoglobin content of the corpuscles is reduced to a far greater extent than is the number of red blood-corpuscles themselves. Thus the average of the fifty-five estimations gives the number of red blood-corpuscles in chlorosis as 3,220,000 per cubic millimetre, and the hæmoglobin content of the corpuscles as 42·2. That is to say, the diminution in the number of corpuscles is about 38 per cent. of the normal, but the diminution in the amount of hæmoglobin in each corpuscle that remains is about 58 per cent. These figures accord well with the fact that in no inconsiderable number of cases oligocythæmia is absent, and the anæmia is therefore entirely due to oligochromæmia.

So far as the chemical composition of the blood is concerned,

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[1] Some complication is introduced in this average by the fact that many of the estimations were made while the patients were in hospital and were improving as the result of treatment.

Biernacki finds that in chlorosis the percentage of water is increased, the chlorine is, as a rule, increased, potassium is diminished, sodium is increased, iron is sometimes normal, sometimes diminished. With reference to the red blood-corpuscles themselves, he finds that the percentage of iron is frequently *raised*, whence he concludes that it is not a deficiency in iron but a deficiency in proteid that characterises the blood-corpuscles in chlorosis. In this connection it is interesting to note that Haldane and Lorrain Smith have found that the oxygen capacity of red blood-corpuscles differs greatly in different layers of one specimen of centrifugalised blood (ox, dog). It is possible that this observation may have an important bearing upon anæmia of the chlorotic type.

One point of importance in reference to chlorosis is that recognisable signs of destruction of corpuscles are almost completely absent, whether on microscopical examination of the blood or tissues, or on chemical examination of the urine or other secretions. The anæmia must, therefore, depend upon an insufficient formation of hæmoglobin, though, at present, it is quite impossible to say upon what this peculiarity depends. When the treatment of chlorotic anæmia leads to improvement, it follows, from what has been said, that nucleated red blood-corpuscles are less commonly seen than in other forms of anæmia, and actually, as can be determined by the repeated examination of a case under treatment by iron, the hæmoglobin value of the corpuscles increases to a much greater extent than does the number of the corpuscles. On microscopical examination, therefore, the blood of chlorosis presents a simpler picture than that presented by the blood of almost any other form of anæmia.

A similar condition of the blood to that found in chlorosis, so far as concerns the relatively great diminution in the hæmoglobin content of the red blood-corpuscles, not infrequently occurs in the subjects of syphilis, of tuberculosis, and of malignant new-growths (especially carcinomata). But though under all of these conditions it is perhaps more common to find a chlorotic type of anæmia, *i.e.*, the hæmoglobin content of the corpuscles diminished to a greater degree than the number of corpuscles, yet this is by no means invariably the case. Indeed, von Limbeck expressly says, after describing the various appearances that may be met with in the blood in syphilis, "to my mind there is scarcely a better example than syphilis of the statement that no clinical form of anæmia is characterised by a definite microscopical appearance of the blood" (*loc. cit.*, p. 335). In syphilis, when anæmia is severe, and therefore most commonly in the secondary and tertiary stages of the disease, megalocytes, microcytes, poikilocytes, normoblasts, and gigantoblasts are frequently met with; the white cells of the blood are generally present in normal numbers, even in the severest cases. When anæmia occurs along with early tuberculosis of the lungs (especially if no fever is present), it is commonly of the chlorotic type, and the number of leucocytes present is normal. But when anæmia occurs in later stages of pulmonary tuberculosis, the complications introduced by ulceration, sweating, fever, etc., are so great, that it is almost impossible to make any general statement concerning the condition of the blood, and quite impossible to decide how far the blood change in any particular case depends upon the tuberculosis itself, how far it is due to disturbing intercurrent causes.

In the case of malignant new-growths, the following table (slightly modified from von Limbeck, and collected from various sources) shows the existence of oligochromæmia with the presence of an approximately normal number of red blood-corpuscles per cubic millimetre in cases of carcinoma.

| | | | | |
|---|---|---|---|---|
| (1) Carcinoma involving heart, . . . . | 5,040,000 | red blood-corpuscles per cubic mm. present, with | 80 | p.c. hæmoglobin. |
| (2) Carcinoma of stomach and liver, . . . | 6,184,000 | ,, ,, ,, | 87 | ,, ,, |
| (3) Carcinoma of œsophagus, . | 8,280,000 | ,, ,, ,, | 48 | ,, ,, |
| (4) Carcinoma of stomach, . | 5,085,000 | ,, ,, ,, | 73 | ,, ,, |
| (5) Carcinoma of stomach, . | 3,415,000 | ,, ,, ,, | 34 | ,, ,, |
| (6) Carcinoma of liver, . . | 4,918,000 | ,, ,, ,, | 70 | ,, ,, |
| (7) Carcinoma of stomach, . | 4,732,000 | ,, ,, ,, | 51 | ,, ,, |
| (8) Carcinoma of stomach, . | 6,200,000 | ,, ,, ,, | 76–78 | ,, ,, |

With regard to the effect of complete removal of a malignant new growth upon the percentage hæmoglobin composition of red blood-corpuscles, Laker and Bierfreund have both found that—contrary to what one would expect—the hæmoglobin content of the corpuscles does not rise after recovery from operation is complete, to a higher level than obtained before the new growth was removed. Though Bierfreund's results cover seventy-two cases and are corroborated by Laker, they are so astonishing, especially in view of the fact that the patients markedly improved in health and put on flesh, that further research upon the subject is necessary. The effects of operation for malignant growths upon the number of leucocytes, and the leucocytosis that is commonly present in malignant disease, will be considered later.

Somewhat in contrast with the anæmias in which either the diminution in number of red blood-corpuscles or the diminution in hæmoglobin content of the blood-corpuscles is the predominant characteristic, but not sufficiently distinct to require a separate sub-division of the subject for themselves, are those cases in which low values obtain for both of these factors. The general feature which runs through these cases is mal-nutrition, whether that mal-nutrition be due to constitutional disease or no. Thus in extreme social poverty, where hard work is combined with chronic semi-starvation, anæmia may be so marked that the number of red blood-corpuscles is reduced to below 1,000,000 per cubic millimetre and the hæmoglobin content to less than 20 per cent. So, too, children who are the subjects of rickets or congenital syphilis are liable to present similar conditions of the blood, though to a less marked extent. The same is observed in chronic poisoning by lead and arsenic. Two points are well marked in all these cases: (1) signs of blood destruction are in the main absent, and (2) as the result of proper feeding and medicinal treatment the anæmia rapidly disappears. It seems as if the activity of the blood-forming tissues in these cases were impaired, and in this respect they have much in common with chlorosis. The outlook for a patient suffering from this, as from most other forms of anæmia, can, to a large extent, be determined by a microscopical examination of the blood, for, speaking generally, a case is hopeful in proportion as signs of blood destruction are absent.

(ii.) *Group II.*—**Anæmias in which marked Changes in**

**the Numbers or Characters of the White Blood-Corpuscles are Present.**—The anæmias of Group II. largely resolve themselves into the condition known as "leuchæmia," a name given by Virchow in 1845 to a particular alteration of the blood, and since then applied to the disease or group of diseases in which this blood change is a prominent characteristic. In this country the abnormal condition of the blood, along with the changes in certain tissues which accompany it, were called "leucocythæmia" by Hughes Bennett, who described them almost synchronously with Virchow, and at the present time this name is frequently employed.

A. **Leuchæmia.**—In leuchæmia the number of leucocytes is not commonly increased to such an extent that the blood can even approximately be termed "white," though in very severe cases it may hardly stain a handkerchief. Often, however, it has the appearance of a mixture of blood and pus; indeed some of the earliest observers regarded the condition as a "suppuration of the blood." In any case, microscopical examination shows that the number of leucocytes is enormously increased. One leucocyte to ten red blood-corpuscles is very usual, one to five not uncommon, and cases have even been known in which the leucocytes outnumbered the erythrocytes. From 100,000–500,000 leucocytes per cubic millimetre may be regarded as about the extremes in ordinary well-marked cases of leuchæmia, though in some cases the higher limit is exceeded. The red blood-corpuscles are diminished in numbers, but by nothing like the same amount as the leucocytes are raised; a diminution to 2,000,000 per cubic millimetre may be regarded as the outside limit, unless it be in very exceptional cases. Poikilocytosis, Maragliano's necrobiotic changes of red blood-corpuscles and nucleated red blood-corpuscles are met with in greater or less numbers according to the severity of the anæmia.

The pathologico-anatomical changes of tissues that are found to accompany these alterations in the composition of the blood concern (1) the spleen, (2) the lymphatic glands, (3) the medulla of bone, that is to say, adenoid tissue and bone-marrow. According as the pathologico-anatomical change is more marked in one or other of these situations, we may speak of a splenic leuchæmia, a lymphatic leuchæmia, a medullary leuchæmia ; but as a matter of fact these forms of leuchæmia are not sharply defined from one another, and in a case of leuchæmia, anatomical changes are commonly to be found in all three situations, though to a different degree in each. The commonest form of leuchæmia is the spleno-medullary ; lymphatic leuchæmia is much rarer, and but very few cases of pure medullary leuchæmia have been observed, though one or two have been recorded in literature (Askanazy). In all cases the affected tissues are profoundly altered, and the principal change consists in an enormous increase in size of the part. Thus in spleno-medullary leuchæmia the spleen may attain a weight of eighteen pounds, though six pounds is nearer the average, and in lymphatic leuchæmia the glands become as large as walnuts. Where the medulla of bone is involved there are signs, not of hypertrophy it is true, but of increased vascularity, and a larger number of cells is present than normal.

*Charcot's Crystals.*—Besides the cellular constituents of leuchæmic blood there are also frequently to be found in blood taken from the patient during life, the so-called Charcot's crystals. These bodies, the chemical composition and the origin of which is not known, have been described either as octahedra or as hexagonal pyramids. They are minute bodies that are often found adherent to leucocytes, and for this reason Zenker considers that they originate from those cells. Westphal obtained them by puncture from the spleens of two leuchæmic patients and thinks that they are formed in this organ. Most authors regard them as being of a semi-proteid nature and as having separated from the blood-plasma. It is said that they are to be found in the normal marrow of bone. Charcot's crystals, however, are not always seen in leuchæmic blood; competent observers, such as von Limbeck and von Jaksch, have failed to discover them.

As the result of treatment, especially by arsenic, and also when an intercurrent acute infective disease has attacked a leuchæmic patient, the number of leucocytes is seen to undergo a marked diminution. With reference to the latter point, there is a considerable amount of evidence that such diseases as typhoid fever, influenza, and septic disease of various kinds, when affecting leuchæmic patients, are accompanied and followed not only by a diminution in number of the leucocytes in the blood but also by a diminution in size of the spleen and lymphatic glands.

B. **Pseudo - leuchæmia.** — Pseudo - leuchæmia, Hodgkin's disease or lymphadenoma, is a pathological condition which agrees with leuchæmia in that it is associated with blood changes largely affecting the leucocytes. In it also both spleen and lymphatic glands are enlarged, and if—as is usual—the splenic enlargement is not great, while the enlargement of the lymphatic glands is well-marked, there may be considerable difficulty from macroscopic examination in differentiating pseudo-leuchæmia from the leuchæmia of the lymphatic type. Moreover, there is the further difficulty that it is uncertain whether under the same name one and the same pathological process or more than one is included. Many authors include sarcomatosis of lymphatic glands under pseudo-leuchæmia, indeed " lymphosarcoma " is one of the many names whereby pseudo-leuchæmia is known on the Continent. A minority of Continental authors (Billroth, Kundrat), however, separate lymphosarcoma from lymphadenoma or Hodgkin's disease, and this is the view taken by most of the clinical pathologists in this country. Clinically, there seems to be a difference between the two conditions, though, no doubt, intermediate forms are found. There is growing up a belief that lymphadenoma may ultimately be shown to depend upon a micro-organism, and, therefore, to be an infective disease, but though bacteria have been described in such cases by several authors, the evidence they offer is inconclusive at present.[1] It is because the term " pseudo-leuchæmia" does not commit one in any way that it is adopted here.

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[1] Personally the author inclines towards the belief that lymphadenoma (*i.e.*, Hodgkin's disease) must be separated from lymphosarcoma, and principally—as yet—because the macroscopic pictures are so different. That there may be a similarity of blood state in lymphadenoma and in lymphosarcoma, so far as number of colourless cells is concerned, cannot, in view of the uncertainty of the microscopical appearances of blood in either case, be regarded as an argument either for fusion or for differentiation. Nor can the fact that in lymphosarcoma the blood commonly shows a larger number of colourless cells than when sarcoma is situated in other regions than the lymphatic glands, be urged against the amalgamation of lymphosarcomata with other sarcomata, for it might reasonably be expected that, when lymphatic glands are the seat of sarcoma, a larger proportion of colourless cells than usual would be washed into the blood by way of the

The general blood changes in pseudo-leuchæmia, it may easily be imagined, are very variable, indeed in some cases in which from clinical evidence one would expect to find the most common change, viz., an increase in number of leucocytes, the number of leucocytes is normal, and the anæmia which exists is due entirely to a diminution in number of erythrocytes and a diminution in their hæmoglobin content, both of which run on parallel lines. Nevertheless pseudo-leuchæmia is generally associated with a great increase in the number of leucocytes, though an excessive increase, such as is seen in true leuchæmia, is wanting. One leucocyte to forty or fifty erythrocytes is a far commoner proportion. As will be seen immediately, the characters of the leucocytes present in leuchæmia and pseudo-leuchæmia are also different; a microscopical examination of the blood suffices to distinguish pseudo-leuchæmia from even lymphatic leuchæmia, which clinical examination often fails to do.

(iii.) **Varieties of Leucocyte present in the Anæmias.**—The variety of colourless corpuscle that is multiplied to cause the increase of leucocytes present in different cases of anæmia, and particularly in the anæmias of Group II., is not always one and the same. Speaking generally, the increase is brought about by addition to the number of finely granular oxyphil (polynuclear, neutrophil) cells, but in some cases it is the lymphocytes, in others the coarsely granular oxyphil (eosinophil) cell that forms the bulk of the increase, while in most cases there is not a numerical increase of one variety alone but of all varieties.

In the so-called secondary anæmias (by which is meant anæmias subsequent to hæmorrhage, or to the establishment of some chronic disease, or to the development of a malignant tumour), where an increase in the number of leucocytes accompanies the anæmia, the cells are almost entirely of the finely granular oxyphil type. On the other hand, in lymphatic leuchæmia the

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thoracic duct. The whole question depends upon whether the lymphocytes and hyaline cells in the blood in lymphosarcoma are true leucocytes (lymphocytes) or whether they are sarcoma cells, and upon this point it is impossible at present to dogmatise.

increase in number of leucocytes is due to the presence in the blood of an enormous number of lymphocytes; in fact it has been suggested that this condition should be termed "lymphocythæmia." In spleno-medullary leuchæmia there is a large increase of leucocytes generally, but the increase to such an extent concerns hyaline (large uninuclear) cells and coarsely granular oxyphil cells that the finely granular oxyphil cells are *relatively* diminished. In pseudo-leuchæmia it is found that increase of leucocytes means relative as well as absolute increase of finely granular oxyphil cells and of lymphocytes, but that there is relative diminution of coarsely granular oxyphil cells.

In some cases, colourless cells not of the ordinary types are present in the blood; this is particularly the case in spleno-medullary leuchæmia, where the number of atypical cells in the blood is very considerable. Some of these are large cells having a single large round nucleus and coarse granules which stain with acid dyes; they are similar in many respects to cells found in normal red bone-marrow, and by some authors are termed "myelocytes," but it is better to speak of them as "atypical" oxyphil or eosinophil cells. Other large cells present in the blood in spleno-medullary leuchæmia show no granules, but have a nucleus which almost fills the cell body and is poor in chromatin; these may be called "atypical" hyaline cells. Cells very similar to these last are also found in normal bone-marrow.[1] Sometimes cells are found with large coarse basophil granules—the so-called Mastzellen. These cells, as has been said, are normally only found in connective tissue; even when found in the blood of spleno-medullary leuchæmia, they are far less commonly present than the other atypical cells which have been mentioned. They have never been found in the blood in any other pathological condition.[2]

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[1] According to Cornil and Ranvier and Müller these cells in the blood have originated from bone-marrow and they call them "medullary cells" (céllules médullaires, Markzellen). As a matter of fact, "Markzellen" include both atypical eosinophil and atypical hyaline cells. Upon the subject of blood and medullary changes in leuchæmia and pernicious anæmia, Muir's papers should be consulted.

[2] So-called splenic anæmia or "Splénomegalie," in which the spleen is enlarged and anæmia is intense, but in which the hæmal changes are similar to those in pernicious anæmia, is too little known to call for more than passing notice here.

(iv.) **Sources of Abnormal Blood-Corpuscles in Anæmia.**—It is now necessary to consider the sources of the various abnormal cells that are observed in different anæmic conditions. From the commencement poikilocytes and forms that are obviously degenerative, microcytes, and megalocytes may be left on one side, for to them reference has already been made (p. 147). The cells, therefore, with which we shall be concerned in the following paragraphs are nucleated red blood-corpuscles, normoblasts, megaloblasts, leucocytes, and the atypical forms of leucocytes which are found in leuchæmia.

The question before us resolves itself into a discussion of the modes and seats of blood-corpuscle formation, and it is impossible to consider this highly controversial subject in detail here. But a short sketch must be given, firstly, because some of the cells mentioned are found when regeneration of blood is taking place, and therefore the process, though it is strictly physiological, comes to have a special interest in pathology, and secondly, because in that way it is possible to throw some light on the ætiology of the leuchæmias.

*Formation of Red Cells in Normal Life.*—The seats of blood formation in earliest embryonic life can hardly be differentiated, but two points with reference to the corpuscles are of importance, and admit of no doubt: 1, all the red blood-corpuscles are nucleated; 2, the colourless blood-corpuscles make their first appearance later than the red blood-corpuscles. In later embryonic life, blood formation takes place in the medulla of bone, the spleen, the liver, and lymphatic glands. In fœtal red medulla of bone are to be found: (1) nucleated red blood-corpuscles, (2) medullary cells (Markzellen, Céllules médullaires), (3) large, coarsely granular oxyphil cells, (4) enormous giant cells, some of which are osteoclasts, (5) Mastzellen. In fœtal spleen-pulp are normal, non-nucleated red blood-corpuscles, nucleated red blood-corpuscles, and large numbers of lymphocytes. In fœtal lymphatic glands, small mono-nuclear lymphocytes are present in large numbers. There is reason, therefore, from a histological standpoint, for regarding the bone-marrow as being the chief seat (but not the only one) of formation of red blood-corpuscles in the embryo, the spleen and the lymphatic glands as the seat of formation of leucocytes. As embryonic life goes on, the number of nucleated red blood-corpuscles diminishes, that of non-nucleated red blood increases. It is agreed by almost all authors that there is a direct change of the former into the latter, but where this change takes place, and whether the normal red blood-corpuscle is produced by disappearance of the nucleus within the nucleated red blood-corpuscle (Bizzozero, Neumann), or by an extrusion of the nucleus which itself becomes the normal red blood-corpuscle (Rindfleisch, Howell), is uncertain. According to Ehrlich, both of these modes of transformation occur,—extrusion in the case of the production of normal erythrocytes from normoblasts, disintegration of the nucleus within the cell in the production of megalocytes from megaloblasts.

In adult life, red blood-corpuscles are commonly regarded as arising from the nucleated corpuscles holding hæmoglobin that are constantly found in normal red medulla of bone ; these cells are often seen undergoing mitotic division. There is the same uncertainty in adult life as in the embryo as to the direct method whereby the non-nucleated is formed from the nucleated corpuscle.[1] Whether the spleen takes any share in the formation of red blood-corpuscles in the normal adult is doubtful. Some authors (Neumann and his school) deny to the spleen any such function ; Rindfleisch, on the other hand, regards the spleen as the chief seat of hæmatopoiesis ; Löwit considers that spleen and medulla of bone take approximately equal parts in the process. The greater number of authors, however, take up an intermediate position and regard the hæmatopoietic function of the spleen (which undoubtedly obtains in embryonic life) as being latent in adult animals and man, but ready to be woke into activity whenever there is a necessity for rapid regeneration of blood.

As to the relation between erythrocytes and leucocytes Müller believes that both arise from one common mother-cell in adult life, Löwit that erythrocytes and leucocytes arise from two different kinds of nucleated cell, neither of which contains hæmoglobin, and which he has called "erythroblasts" and "leucoblasts." Since in the embryo red blood-cells are present at a time when leucocytes have not yet made their appearance, a twofold source of origin seems the more probable. There is no evidence that red blood-corpuscles directly originate from leucocytes, though this view was largely held at one time.

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[1] According to Hayem, the non-nucleated red blood-corpuscles are formed from blood-platelets (Hayem's hæmatoblasts), and their seat of formation is the circulating blood ; the nucleated red blood-corpuscles he regards as being formed in the hæmatopoietic tissues, especially the red medulla of bone.

*Formation of Leucocytes in Normal Life.*—The seat of leucocyte formation in adult life constitutes at the present time one portion of the whole controversy as to the relationship of the different varieties of leucocyte. If the leucocytes that one finds circulating in the blood are, as some authors believe, but stages in the life history of one kind of cell, the youngest recognisable form of which is the lymphocyte, then the matter is comparatively simple, for in the lymphatic glands are enormous numbers of typical lymphocytes, and the numerous mitotic figures that are found in the cells inhabiting the glands are evidence that cell division is going on here with great rapidity.

But though it is agreed on all hands that the lymphatic glands are a highly important source of leucocytes, and though the lymphocyte is usually regarded as a young form of any variety of leucocyte, many authors find a difficulty in accepting the view that all leucocytes of the blood have a common origin. This is partly because the distribution of the different varieties of wandering cell in different species of animal is not uniform, partly because the so-called transitional forms are never observed except after the cells have been killed, but principally because the morphological appearances and the histo-chemical reactions of the cells are not the same, and because the functions of the cells, as will be seen later, in many cases seem to be absolutely different. Virchow long ago regarded the small leucocytes as arising from the lymphatic glands, the large leucocytes as arising in the spleen, and at the present day, besides lymphatic glands and spleen, the bone-marrow is regarded as certainly, and the interstitial connective tissue as most probably, a further seat of leucocyte formation.

*Origin of Leucocytes in Leuchæmia.*—We may now consider the origin of the abnormal cells found in the blood under different anæmic conditions. When enquiring into the origin of the leucocytes that are present in enormous numbers in leuchæmic blood, especially when the disease is of the spleno-medullary type, it is striking that many of the cells present in the blood correspond closely, if not exactly, to cells normally found in the red bone-marrow of the embryo. Moreover, the fact that the cells in the bone-marrow in spleno-medullary leuchæmia are greatly increased in numbers, suggests that the cause of the leuchæmia is a hyperactivity of the bone-marrow, and that the spleen and the lymph-glands aid in the process. This view is very commonly held, and, as has been said, certain cells found in the blood are definitely called "myelocytes," "medullary cells," "céllules médullaires," "Markzellen," while the expression "myelogenous" is used in connection with particular varieties of leuchæmia. It is quite obvious, however, that the medullary, splenic, lymphatic, and hæmal changes may be simultaneous expressions of one and the same cause as yet unknown. It is, therefore, advisable to use terms which do not finally dispose of a question which cannot as yet be considered as beyond doubt, and for this reason the expressions "atypical oxyphil (eosinophil) cell" and "atypical hyaline cell" have been used for "myelocyte," and "medullary" has been used for "myelogenous" in the preceding pages. In this matter the author follows Kanthack.

*Origin of Red Blood-Corpuscles in the Anæmias.*—The cellular changes in leuchæmic blood, which are principally confined to the wandering cells, and are distinctly pathological, must be sharply separated from the cellular changes that occur in other anæmic conditions and are evidence of a physiological regeneration of blood. In all cases of anæmia, of whatever kind, evidences of blood regeneration are to be found to a greater or less extent, and in all cases in which they are well-marked the bone-marrow, at all events, shows a change. Marrow that is normally yellow, becomes red, highly vascular, and highly cellular. In particular it contains numbers of nucleated red blood-corpuscles, and there can be no doubt that the nucleated red blood-corpuscles present in the blood in severe anæmia—especially in anæmias in which a great diminution in the number of red blood-corpuscles occurs—

arise from, or are identical with, the nucleated red blood-corpuscles in the bone-marrow. Whether the spleen takes a share in normal hæmatopoiesis, we have already said, is uncertain, but the balance of evidence derived from extirpation of the spleen, from histological examination of the spleen in experimental anæmia, and from comparison of the blood in splenic artery and vein, seems to support the view that, though this organ probably takes no share in the formation of red blood-corpuscles in normal adult life, it reverts in part to its embryological functions whenever severe anæmia is present.

(v.) **Effects of Anæmia upon the Body.**—The effect of anæmia upon the body at large, and upon the manner in which the various organs exercise their functions, is a subject upon which very little can be said. The greater part of the symptoms produced are those due to insufficiency of hæmoglobin, and, as a consequence, pallor is characteristic of the condition. Since, too, hæmoglobin is intimately bound up with the oxygen-carrying function of the blood, it follows that in anæmia the supply of oxygen to the tissues is diminished. The result of this is threefold.

1. The respiratory centre in the medulla oblongata is affected. The activity of this centre is increased whenever the amount of oxygen which it receives in the blood is diminished below a certain point. Under normal circumstances the amount of oxygen in the blood is sufficiently great that small demands made by other parts of the body, and especially the muscles, can be met without lowering the amount of oxygen in the blood to such an extent as to lead to undue activity of the respiratory centre. For example, a healthy person can run upstairs without panting. But in anæmia the case is different, in that the blood carries an amount of oxygen which, in severe cases, is barely sufficient to ensure a normal rate of respiration when the patient is at rest. The least exertion, therefore, being accompanied by an increased demand for blood on the part of the muscles concerned, and by an active dilatation of their blood-vessels, reduces the amount of blood, and therefore of oxygen, which the respiratory centre receives below the point at which increased activity is

called forth, and hence in severe anæmia moderate exertion is accompanied by a great increase in the rapidity of respiration. To continue the example given above, a chlorotic girl complains of shortness of breath on mounting stairs.

2. As the result of deficient oxygenation, fatty changes take place in various organs. It will be seen later that perhaps the chief cause of fatty change is deficiency in the supply of oxygen. In the case of chlorotic girls, the amount of fat throughout the body generally, but especially in the subcutaneous connective-tissue, is considerable, and the plumpness of these persons is almost characteristic. In the case of pernicious anæmia, fatty degeneration is often very extensive ; it affects in particular the musculi papillares of the heart and causes them to take on a peculiar macroscopic appearance which is known as "tabby-cat striation." That the fatty change in the heart muscle must be regarded as an expression of the deficient nutrition and oxygenation of the heart, there can be no doubt, for the blood state is such that nutrition and oxygenation cannot possibly be carried out in a normal manner. But, besides its dependence upon deficient nutrition and oxygenation, it is possible—even probable—that the change is in part due to the action of some toxic substance circulating in the blood. It has already been said that the blood changes in pernicious anæmia are by many authors regarded as due to an unknown toxin, and so far as fatty changes are concerned, it is known that many poisons, bacterial and non-bacterial, lead to fatty degeneration. We shall probably not err greatly if we regard the fatty change that occurs in various situations in all cases of prolonged anæmia as due to the deficient supply of nutrition and oxygen, aided in some cases by a direct poisoning of the tissue in question.

3. It is noticed that severe anæmia, especially when it is suddenly produced, as, for example, by severe post-partum hæmorrhage, is accompanied by the onset of epileptiform convulsions. These, it has been experimentally proved, are associated with anæmia of the brain.

Besides breathlessness, fatty changes, and epileptiform convulsions, anæmia, if severe and prolonged, is very commonly associated with small amounts of œdema. In the author's opinion, this œdema is essentially dependent upon deficient nutrition of the tissues, but the question will be discussed along with other forms of œdema in the following chapter.

Hæmorrhages, scanty or profuse, whether subcutaneous or from mucous surfaces, are not uncommon in severe anæmia of whatever kind. It is not easy to understand how these hæmorrhages are brought about. In view of the fact that, at all events in leuchæmia and in anæmia due to actual hæmorrhage, the coagulability of the blood is increased, the possibility that hæmorrhages seen in anæmia are due to deficient coagulability of the blood may be set on one side. The most reasonable explanation left is that the blood-vessel walls are altered. In the arteries of anæmic persons it is known that fatty changes of the intima are common, and it is possible that abnormality of the blood produces some alteration in the capillaries and arterioles whereby they rupture with extreme ease. But whether this alteration exists, and whether, if it exists, it is ultimately due to starvation or to the direct action of some toxic substance, it is impossible to say. In the latter case, the hæmorrhages would be in some degree comparable with those frequently seen in severe cases of infective disease.

IV. **Leucocytosis and Leucopenia.**—Increase and diminution in the number of leucocytes present in the blood are known under a variety of conditions, which do not come under the heading of anæmia; we have already mentioned the existence of a physiological leucocytosis and a physiological leucopenia. During the last few years leucocytosis and leucopenia have been shown to play a very prominent part in many pathological processes; they have been studied particularly in connection with inflammation and immunity. The theoretical considerations concerned with variations in the number of leucocytes are so important that they demand special attention, and will be dealt with along with inflammation and infection. Here we shall confine ourselves to certain broad statements of fact.

The best known pathological conditions accompanied by a definite leucocytosis are those in which the body is the subject of inflammations of various kinds, of some acute infective disorders, or of malignant new-growths; leucocytosis also occurs to a marked degree after hæmorrhage, and when various chemical substances are introduced into the circulation. The last-mentioned variety of leucocytosis will be considered along with the phenomenon known as "chemiotaxis."

The characteristic point about leucocytosis is that it is essentially a temporary condition. In acute infective disorders of man it usually shows itself during the febrile stages, and the increase principally concerns the finely granular oxyphil cells. In croupous pneumonia the number of leucocytes is frequently doubled or trebled, and not uncommonly the curve given by the number of leucocytes in the blood runs parallel with the curve given by the temperature of the patient. Though in the majority of cases leucocytosis occurs, it is not invariable; this is an important point, for when leucocytosis is well-marked the case will generally run a favourable course, but if there is leucopenia the prognosis is not so hopeful. Immediately before the crisis the leucocytosis is commonly at its height, and in this disease, as also in erysipelas, the leucocytosis lasts only a short time after the temperature has fallen to normal. In scarlatina, on the other hand, the leucocytosis apparently persists long after all signs of the disease have disappeared. In uncomplicated typhoid fever, according to von Limbeck, hæmal leucopenia is always present, and when, as is sometimes the case, leucocytosis is found, it is due to some pneumonic or suppurative complication. Uncomplicated malaria and tuberculosis are unaccompanied by any alteration in the number of leucocytes present in the blood. Asiatic cholera is of some interest in this connection, since the marked leucocytosis, which, according to Biernacki, is seen during the algid stage of the disease, does not appear to be of the same favourable prognostic value that it is when it occurs in croupous pneumonia.

With regard to the effect of malignant new-growths, both carcinoma and sarcoma are liable to be accompanied by leucocytosis, but the leucocytosis is neither so constantly present nor so considerable when the new-growth is carcinoma. In the case of carcinoma with leucocytosis, though the number of leucocytes present per cubic millimetre of blood is usually about 10,000, as many as 80,000 per cubic millimetre have been known. Grawitz has shown that in rabbits intra-vascular injection of an extract of cancerous material leads to great leucocytosis, and it is possible that a softening and absorption of cancerous material may explain the excessive degree of leucocytosis in human cases, but this cannot at present be regarded as certain. Leucocytosis along with sarcomata is very constant and well-marked, the average number of leucocytes present being about 12,000 per cubic millimetre, but this figure is often greatly exceeded. In the case of round cell sarcomata, I think there is always a certain amount of doubt whether some of the colourless cells in the blood may not be sarcoma cells. Removal of a malignant new-growth appears to exert a marked effect upon the leucocytosis, and in this respect affords a great contrast to the absence of effect that removal of a malignant new-growth has upon the number of red blood-corpuscles (*cf.* p. 167). This is well shown by the following two of several cases recorded by Hayem. Before operation in a case of cancer of the mamma the number of leucocytes present per cubic millimetre of blood was 21,700, after complete healing of the wound it was found to be 6,200 per cubic millimetre. Before operation in a case of osteosarcoma the number of leucocytes per cubic millimetre of blood was 11,250, after healing of the wound it was 5,270.

After hæmorrhage, especially if severe, a leucocytosis is seen which may be well marked. It begins to show itself 10–15 minutes after the loss of blood has occurred, and often lasts for several days. Hoche has shown that one of the primary effects of hæmorrhage upon the lymphatic circulation is an immediate but short increase in the rate of lymph flow. It is probable that a portion of the leucocytosis depends upon the fact that large numbers of leucocytes are washed from the lymphatic glands into the circulation, but this can hardly account for the persistence of leucocytosis over several days, since in Hoche's experiments the lymph flow returned to the normal, if it did not actually fall below normal, after five or six minutes. It is possible that some obscure—possibly septic—process plays part in causing the leucocytosis, but in any case it is certain that neither the trauma nor the actual loss of blood can explain it in full.

Leucopenia is a condition concerning which but little is known. Löwit has shown that gradual tying down of a rabbit causes a marked leucopenia which especially affects the hyaline cells and lymphocytes (uninuclear cells). On the other hand, if the animal be tied down suddenly, or shock be produced by vigorously shaking it or striking it on the head, there is a rapid leucopenia which affects all kinds of leucocytes. The leucopenia in the first case Löwit ascribes to arrest of development of leucocytes in the blood-forming tissues, that which occurs in the second case he regards as due to leucolysis or an actual destruction of leucocytes. Similar results may be brought about by cooling the body surface. Sherrington found in the case of severe local inflammations that there is a diminution in the number of coarsely granular oxyphil cells in the blood. This is a matter of importance, in view of the fact that large numbers of these cells are found at the seat of inflammation.

Both leucocytosis and leucopenia will call for additional remarks in connection with the subjects of inflammation, chemiotaxis, susceptibility, and immunity.

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# CHAPTER VI.

## The Pathology of the Blood (*continued*)—with especial reference to the Blood-Plasma, Œdema, and Absorption.[1]

*Synopsis.*

- I. The Chemical Composition of Blood-Plasma and Serum.
- II. Filtration in Pathological Problems.
- III. Osmosis in Pathological Problems.
- IV. Lymph Formation :
  - (i) Ludwig.
  - (ii) Heidenhain.
  - (iii) Starling.
  - (iv) Hamburger.
  - (v) The Author.
- V. Œdema Formation :
  - (i) Clinical Varieties of Œdema.
  - (ii) Composition of Œdema Fluids.
  - (iii) The Pathology of Œdema :
    - (*a*) Older Views.
    - (*b*) Modern Views.
  - (iii) The Pathology of Œdema :
    - (*c*) The Author's View.
      - ($\alpha$) Inadequacy of Physical Explanation.
      - ($\beta$) Importance of Tissues in Œdema Formation.
      - ($\gamma$) Importance of Blood-Vessels in Œdema Formation.
      - ($\delta$) Explanation of Distribution of Œdema.
      - ($\epsilon$) Source of Œdema Fluid.
      - ($\zeta$) Absorption of Œdema Fluid.
        - (1) Part played by Lymphatics.
        - (2) Part played by Blood-Vessels.

Before dismissing the subject of the pathology of the blood it is necessary to consider the relationship between the blood-plasma and the tissues somewhat in detail, since under a large number of pathological conditions there is found in the tissues and the serous cavities an excessive amount of fluid which can only have collected there because the normal equilibrium between blood, tissues, and lymphatics has been disturbed. This general condition, which is known under the names of "œdema," "dropsy," "anasarca," etc., will, however, be left on one side until the physical processes of filtration and osmosis have shortly been discussed. This course becomes necessary, because the whole question of œdema is intimately bound up with the physiological question of lymph formation, and in the controversy as to the cause of lymph formation the processes of filtration and osmosis play a prominent part.

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[1] Pathological conditions in which the blood-plasma is altered in composition, *e.g.*, in diabetes mellitus, will not be considered in this chapter, but along with the special diseases in which the blood changes occur. Such a course relieves the reader of cross-reference.

At the very outset it must be pointed out that, though it is possible to examine the blood-corpuscles, and especially the leucocytes, in a living, and therefore in an approximately normal condition, this is not the case with the blood-plasma. Coagulation of the blood, which of course essentially concerns the blood-plasma, supervenes so quickly after removal of the blood from the body, that observations upon normal blood-plasma are hardly to be made. There is no doubt that, by the addition of oxalate or citrate of potash or soda to blood immediately on shedding, it is possible to keep it fluid for a long time after removal from the body, and that the addition of albumoses (commercial peptone, snake venom, bacterial toxins) to the still-circulating blood, whether experimentally or in the course of disease, materially retards the onset of coagulation. But under these circumstances the blood-plasma that is obtained after precipitation of the corpuscles by centrifugalising or rest, is not normal blood-plasma. The case is even worse if blood-serum obtained after coagulation and contraction of the blood-clot be made the subject of investigation, for here it is obvious that one is dealing with a fluid that is absolutely foreign to the normal body. It is only with great caution, therefore, that experiments performed with blood-plasma or serum outside the body may be used to explain processes that go on within the body. Information obtained in this way is, however, in a considerable number of cases the only information at our disposal; but sometimes, fortunately, it may be used without risk of serious error.

**I. The Chemical Composition of Blood-Plasma and Serum.**—It is impossible to give here a detailed account of the chemistry of the blood-plasma and serum, but it is necessary, in view of the physical processes which are immediately to be discussed, to bear in mind that blood-plasma and serum are albuminous fluids, holding certain crystalloid substances in solution. The proteids of serum are serum-globulin and serum-albumin; the amounts of these two substances present vary in different species of animal, whether warm-blooded or cold-blooded. In man the total amount of proteid present in the serum is on an average 7·6 per cent., of which 3·1 per cent. is serum-globulin, 4·5 per cent. is serum-albumin (Hammarsten). In the horse and ox, though the total amount of proteid present is about the same, the relations of serum-globulin and serum-albumin are reversed, so that in these animals the blood-serum contains more globulin than albumin. The proteid content of the blood-serum is remarkably constant, though of course the percentage diminishes whenever the amount of water in the blood is increased or when there is a great loss of proteid, as, for example, in lardaceous disease of the kidney, and increases when there is a great loss of water from the blood, as, for example, in Asiatic cholera. Inorganic crystalloids are present in blood-serum and plasma to about ·8 per cent., of which ·5 per cent. consists of sodium chloride. The remainder is composed of sodium, potassium, calcium, and magnesium in combination with sulphuric, carbonic, and phosphoric acids, and with chlorine. To litmus, blood-plasma and serum are weakly alkaline. Excepting in the fact that it contains a far smaller amount of proteid, it is practically impossible to give any distinguishing chemical feature between blood-plasma and lymph: in particular, the amounts of crystalloid substances in the two fluids are approximately the same.

**II. Filtration in Pathological Problems.**—When considering filtration in connection with lymph and œdema formation it must be remembered that the process cannot be the same as occurs in ordinary filtration outside the animal body. When filtering a solution of any crystalloid in the ordinary way, with air on the other side of the filter, the amount of fluid which passes through the filter varies directly with the pressure under which the solution is placed, and the degree of concentration attained by the filtrate may be either equal to or less than the degree of concentration of the filtering fluid, but it can never be greater. But in the animal body there is no region where such a condition could easily obtain except the lungs, and hence it is necessary, in investigating filtration—especially in connection with lymph formation—outside the body, to replace air on the distal side of the filter by a liquid. This has been done by Cohnstein, and though it is difficult to accept his results unreservedly, owing to the fact that when two fluids are separated by a membrane, at least two other physical processes, dialysis and osmosis, are going on in addition to the filtration, and therefore complicate the final result, yet Cohnstein's work shows that it is very unsafe to argue from ordinary filtration to filtration within the animal body. Moreover, Runeberg and others showed that when filtration is taking place under ordinary circumstances, variations in the pressure to which the filtering fluid is exposed have different effects upon the percentage composition of the filtrate, according as the filtering fluid contains a colloid or a crystalloid. In the case of a crystalloid, Runeberg found that the percentage composition of the filtrate varies directly with the pressure under which filtration is taking place, but in the case of a colloid, the percentage composition of the filtrate varies inversely with the pressure under which filtration is taking place. Cohnstein found that the concentration of the transudate varies directly with the pressure *against* which filtration is taking place; but, as has been said, it is difficult to accept his results as being an expression of the effects of filtration alone.

III. **Osmosis in Pathological Problems.**—The physical process of osmosis has of late years been very prominently brought forward in connection with lymph and œdema formation. From a physical point of view it was originally investigated by Graham in 1854, and he studied the process along with dialysis in the case of a variety of animal and artificial membranes. Osmosis is very commonly confused by biologists with diffusion and dialysis, but the physicist recognises them as three absolutely distinct processes, though not infrequently two, or even all three of them, are taking place together. The differences that obtain between the three processes can best be shown by examples.

**Diffusion.**—If a 20 per cent. solution in water of magnesium sulphate be placed in a vessel, and on it be carefully placed an equal quantity of distilled water, there will be recognisable at first a fairly well marked line of demarcation between the two different fluids. In course of time, even though the vessel be kept at complete rest, it will be found that the line of demarcation is lost, and that the whole contents of the vessel consists of a uniform solution of 10 per cent. magnesium sulphate. The mixture has taken place by *diffusion*, and in this process no membrane is concerned. In dialysis and in osmosis, on the other hand, a membrane is invariably concerned.

**Dialysis.**—If a 20 per cent. watery solution of magnesium sulphate be placed on one side, A, of a permeable membrane, and distilled water be placed on the other side, B, it will again be found after a time that the composition of the fluid on either side of the membrane is 10 per cent. magnesium sulphate, but it is obvious in this case that molecules of the crystalloid in A must have passed through the membrane into B. This process is *dialysis*.

**Osmosis.**—If a crystalloid in solution be separated by a *perfect semi-permeable membrane* from distilled water (the crystalloid being on the side A and the distilled water on the side B of the membrane), it will be found (1) that molecules of water pass through the membrane from B to A until a certain pressure has been reached on the side A of the membrane, and that then the passage of water molecules through the membrane ceases, (2) that during this time no molecule of the crystalloid passes through the membrane from A to B, (3) that the pressure reached in A before passage of water molecules through the membrane from B to A ceases, is approximately the same for all chemically indifferent[1] substances in equimolecular solution.[2] This process is *osmosis.*

The pressure that is reached before osmosis, *i.e.*, the passage of water molecules through the membrane, ceases, is, in the case of a normal[3] solution of an indifferent chemical substance, approximately 22·5 atmospheres. This pressure is called the *final osmotic pressure* of the substance. When dealing not with indifferent substances but with electrolytes, it is found that the final osmotic pressure is a more or less exact multiple of the value that would be expected from a consideration of the molecular weight. Thus, the molecular weight of sodium chloride is 58·5, and if 58·5 gms. of sodium chloride were dissolved in 1 litre of water, it would be found that the final osmotic pressure of the solution would be not 22·5 atmospheres, as it would be if sodium chloride were an indifferent substance, but about 44 atmospheres. Since the fundamental conception which underlies osmosis is, that it depends upon the number of molecules of the crystalloid present in unit volume of the solvent, and is independent of the size or the density of the molecules, the fact that the final osmotic pressure is nearly double the amount that would theoretically be expected, indicates that the number of molecules (exclusive of the solvent) present in the solution is nearly double that which is indicated by the molecular weight of the substance. That is to say, if $x$ molecules of solid sodium chloride be weighed and dissolved in a certain quantity of water, the number of molecules (exclusive of the water molecules) actually moving about in the solution is approximately $2x$. Now it is obvious that these molecules cannot be molecules of sodium chloride, for only $x$ molecules of sodium chloride were introduced, and it is assumed that the greater number of the sodium chloride molecules when in solution "dissociate" into sodium molecules and chlorine molecules, and that these move about in the solvent independently of one another. In this way the number of molecules in the solution will be approximately double that indicated by the molecular weight of the sodium chloride, and therefore the final osmotic pressure will be approximately double the theoretical value. It is impossible to enter here into the theory of osmosis, but it is actually found that an assumption of dissociation in the case of electrolytes suffices to explain the apparent exception which they offer to the rule, that the final osmotic pressure of all crystalloid substances in equimolecular solution is approximately identical.

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[1] An indifferent substance is one which cannot be electrolysed. Glucose and urea are indifferent substances.

[2] Solutions are said to be equimolecular when the amounts of crystalloid which they contain bear the same ratios to one another as is borne by the molecular weights of the crystalloids themselves. Thus a 1 per cent. solution of urea is equimolecular with a 3 per cent. solution of glucose, a 2 per cent. solution of urea is equimolecular with a 6 per cent. solution of glucose, and so on, because the molecular weight of glucose (180) is three times the molecular weight of urea (60).

[3] A normal solution is one in which molecular weight of the substance in grams is dissolved in 1 litre of water.

Another fact which is of great interest from the point of view of osmosis must be mentioned. It is known that the freezing point of water is lowered when it contains a crystalloid in solution, and that the temperature at which the solution commences to freeze is lower according as the amount of crystalloid which it contains is greater. It has been shown by Van't Hoff and others that in the same way as the final osmotic pressures of indifferent substances in equimolecular solution is identical, so the freezing points of indifferent substances in equimolecular solution are identical. Normal solutions in water of indifferent crystalloids freeze at $-18{\cdot}9°$ C. This discovery is one of very great importance, since the estimation of the final osmotic pressure of a solution is a difficult matter, while a determination of its freezing point is quite easy. Solutions which have the same freezing point, and which, therefore, have the same final osmotic pressure, are said to be isotonic. The terms hypertonic and hypotonic sufficiently explain themselves.

Now, though it is certain that with a *perfect* semi-permeable membrane no molecule of the crystalloid would pass through the membrane, such a condition has hitherto never been obtained. In physical experiments on osmosis, a membrane composed of copper ferrocyanide is used; it is deposited in the interspaces of a porous porcelain cell (similar to those used in electric batteries) by the chemical interaction of copper sulphate solution placed inside the cell, and potassium ferrocyanide solution placed outside the cell. The two solutions penetrate for a certain distance into the wall of the cell, and at their line of junction copper ferrocyanide is formed. For many crystalloids, copper ferrocyanide is a perfect or a nearly perfect membrane, and in any case it is nearer perfection than any membrane that has been devised. But even with copper ferrocyanide membranes, in most cases after a prolonged experiment the crystalloid is to be found on both sides of the membrane; in other words, dialysis has accompanied osmosis. And, indeed, under ordinary conditions and with ordinary membranes, dialysis occurs wherever osmosis is taking place, osmosis occurs wherever dialysis is taking place. But the difference between the two processes is that theoretically osmosis can take place in the absence of dialysis (and practically it can be shown to take place when dialysis is so small as to be negligible), whereas dialysis can never occur in the absence of osmosis, even theoretically.[1]

The first biological investigations in connection with osmosis were made by de Vries, who explained thereby the turgescence of plants. De Vries found that when the cells of the leaves of certain plants, in which the process can easily be watched, are placed in a solution of a crystalloid, the protoplasm shrinks from the cell membrane, remains unaltered, or swells up and distends the cell membrane according to the concentration of the solution. He explained these phenomena by supposing that the cell protoplasm shrinks because water passes from it through the cell membrane into the solution of crystalloid, when the latter is hypertonic as far as the saline constituents of the cell protoplasm are concerned. In the same way the cell protoplasm swells up because water passes into it through the cell membrane, when the saline constituents of the cell protoplasm are hypertonic so far as the solution of crystalloid outside the cell is concerned. In those cases in which neither shrinkage nor swelling of the cell protoplasm occurs, he supposed that the solution of crystalloid is isotonic with the cell protoplasm. By adjusting the strengths of different crystalloid solutions he found that, when different crystalloids are used, the strengths of the solutions in which the cell protoplasm remains unaltered bear constant and definite relations to the molecular weights of the crystalloids used.

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[1] The physical literature of osmosis is chiefly to be found in papers by Van't Hoff, Arrhenius, Ostwald, Raoult, Guldberg and others in the *Zeitschrift für physikalische Chemie*, from its commencement in 1887.

Hamburger applied de Vries's work to the red blood-corpuscles and the blood-plasma and serum, and it is to him that we owe the greater part of our knowledge concerning osmotic phenomena in connection with physiology. Hamburger used the red blood-corpuscles in the same way as de Vries used the vegetable cells. Starting from the well-known fact that blood "lakes" (in other words, that the hæmoglobin leaves the blood-corpuscles and becomes dissolved in the plasma) when water has been added to the blood, he investigated the tonicity of the red blood-corpuscles in terms of solutions of sodium chloride. If a series of tubes be arranged containing solutions of sodium chloride varying in degree of concentration from, say, ·4 per cent. to ·5 per cent., and into each a small quantity of a given specimen of blood be dropped, and, after shaking, the mixture be allowed to stand for twenty-four hours, it will be found that in some of the tubes, *e.g.*, those containing saline solutions from ·4 per cent. to ·46 per cent., the hæmoglobin has left the corpuscles and has dissolved in the saline solution, whereas in the remainder of the tubes this escape of the hæmoglobin has not taken place. This phenomenon may readily be observed, and, according to Hamburger, it depends simply upon a process of osmosis. From Hamburger's point of view in the example given, the solutions whose strength is below ·46 per cent. are hypotonic as regards the red blood-corpuscles, and hence water passes through the wall of the corpuscles into the protoplasm by osmosis, distends the corpuscle, and ultimately leads, by actual rupture or by increasing the permeability of the wall, to a discharge of the hæmoglobin. On the other hand, the solutions whose concentration is greater than ·46 per cent. are hypertonic as regards the red blood-corpuscles, and therefore water leaves them by osmosis through the corpuscle wall. The corpuscle, as a whole, therefore, shrinks, its wall becomes less permeable and the hæmoglobin is retained. The least concentrated solution of sodium chloride in which hæmoglobin is *not* discharged, and the most concentrated solution in which hæmoglobin *is* discharged, Hamburger regards as lying on either side of the concentration which is isotonic for the particular corpuscles under investigation. Besides sodium chloride, Hamburger investigated a variety of other crystalloid substances in solution, and found, like de Vries, that isotonic solutions, as determined by portions of the same sample of blood-corpuscles, bear constant relations to the molecular weights of the crystalloids used.

All kinds of red blood-corpuscles have not the same degree of tonicity. Those of the rabbit are isotonic with a markedly higher concentration of sodium chloride solution than those of man or the dog. Nor even have corpuscles from the same individual always the same tonicity. Thus Hamburger found that the corpuscles from arterial blood have a lower tonicity than those from venous blood. This fact may be correlated with the fact that the specific gravity of the red blood-corpuscles has not one constant value even in the same individual. A certain number of investigations have been made upon the tonicity of the red blood-corpuscles in disease, especially by von Limbeck, but they must be consulted by those interested in the subject in his work upon the *Pathology of the Blood.*

By an extension of his method Hamburger investigated the tonicity of the blood-serum. Having found the tonicity of a certain sample of corpuscles in terms of sodium chloride, he proceeded to dilute the serum whose tonicity he wished to determine with water, until he found the point at which hæmoglobin left the red blood-corpuscles. So far as tonicity is concerned, he concluded that the diluted serum in which hæmoglobin just failed to leave the corpuscles was isotonic with the solution of sodium chloride in which hæmoglobin just failed to leave the corpuscles. The strength of this solution of sodium chloride and the degree to which the serum was diluted being known, a simple calculation enabled him to determine the tonicity of the undiluted serum in terms of sodium chloride solution. The tonicity of mammalian blood-serum estimated in this way and controlled by the freezing-point method varies under different circumstances and in different animals. Speaking generally, Hamburger finds that it corresponds to that of a ·92 per cent. solution of sodium chloride.

By some authors the relations of the blood-corpuscles and the plasma are thought to be purely physical. But in the first place it is remarkable that the tonicity of the red blood-corpuscles is so greatly inferior to the tonicity of the plasma in which they are suspended; on physical principles one would expect that the tonicity should be the same in both. That this is obviously not the case indicates that the relations of corpuscles and plasma are not regulated by osmosis alone, at all events in the sense that osmosis is usually understood at the present day. In the second place, as von Limbeck points out, this view assumes that the red blood-corpuscles have a cell membrane and fluid contents, or at least in their structure approximate to such conditions. This idea of the construction of the red blood-corpuscle is certainly not proved. Whether, too, the hæmoglobin simply lies in the interspaces of the corpuscular network, or actually forms a chemical compound with the corpuscular protoplasm, as is suggested by some authors (Hoppe-Seyler), is uncertain. In the third place, the tonicity of a given specimen of red blood-corpuscles remains constant in spite of great alterations in the tonicity of the blood-serum in which it is suspended. Von Limbeck[1] gives details of an experiment in which serum from one source was divided into three portions. The tonicity of one portion was raised by addition of concentrated sodium chloride solution until it was equal to that of a 1·3664 per cent. solution of sodium chloride; the tonicity of a second portion was lowered by addition of water till it was equal to that of a ·873 per cent. solution of sodium chloride; the third portion, whose tonicity was equal to that of a 1·008 per cent. solution of sodium chloride, was left untouched. Into each of these sera blood-corpuscles from the same sample were placed, and it was found that, in spite of the different tonicities of the three sera, the tonicity of the red blood-corpuscles in each of them was equal to that of a ·56 per cent. solution of sodium chloride. It must, therefore, be concluded that though osmotic phenomena are observable, both in the case of the red blood-corpuscles and in the case of the blood-serum (or plasma), yet the relations between red blood-corpuscles and plasma are not exclusively osmotic according to our present conceptions of the process. How far Hamburger's method and the freezing-point method are reliable for determining the occurrence or absence of osmosis will be discussed later.

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[1] *Loc. cit.*, p. 162.

Having described the physical processes that may be concerned in lymph and œdema-formation, we can now turn to the principal theories that have been put forward in explanation of the undoubted fact that, both in lymph-formation and in œdema-formation, fluid leaves the blood-vessels, in the latter case to such an extent that it collects in the tissues and serous cavities. It will be necessary to consider the theories of normal lymph-formation somewhat in detail, partly because that subject has received more attention than œdema-formation from the experimental point of view, though not attention over a longer period of years, partly because there is reason to believe that the same processes obtain, at all events to a considerable degree, in both cases. Nevertheless, it is impossible to give more than a brief outline of the considerations upon which these theories are based.

IV. **Lymph-formation.**—At the present day two chief views are held as to the mode of lymph-formation. On the one hand, it is held that normally the lymph is separated from the blood by a process akin to filtration, aided by osmotic interchange due to chemical differences between lymph and blood-plasma; this may be called the physical theory of lymph-formation. On the other hand, it is held that normally the lymph is actively secreted by the endothelial cells of the vessel wall; this may be called the vital theory of lymph-formation.

(i.) **The Experiments of Ludwig and his Pupils.**—The physical theory of lymph-formation was elaborated by Ludwig and his pupils; they maintained that lymph-formation essentially depends upon the difference in pressure that exists in the capillaries and in the lymph spaces that surround the capillaries, that, in other words, a portion of the blood-plasma filters through the capillary walls and constitutes the lymph. It was, of course, allowed that the lymph, as found in the lymphatic vessels, does not represent the unaltered fluid that transudes through the vessel walls, for in its passage between the tissue cells some elements are taken from the fluid, others are added to it by the tissue cells themselves. But nevertheless they held that lymph is essentially a filtrate. As a filtrate, too, its quantity was regarded as necessarily dependent upon the difference between intra- and extra-capillary pressure, and, therefore, any means whereby the capillary pressure was raised was accompanied by an increased outflow of lymph. That this was the case, they held, was readily to be seen in the excessive amount of lymph-formation which occurs whenever the venous pressure in a part is increased, and the œdema seen in heart disease was regarded as a complete demonstration of the fact that increased exudation goes hand in hand with increased venous and capillary pressure. A difficulty that was raised by the fact that the fluid which collects in the tissues, as the result of increased venous pressure (when the capillary pressure is greatly raised), is very poor in proteid compared with fluid poured out when the capillary pressure is not increased to so obvious an extent, was largely overcome by Runeberg's discovery that in the filtration of an albuminous fluid through fresh intestine of rabbit, the percentage of proteid in the filtrate varies inversely with the pressure under which filtration is taking place. But from Ludwig's laboratory itself difficulties in the way of Ludwig's views were made known. For Paschutin found that when the arterial dilatation produced in the fore limb of an animal by section of the brachial plexus is further increased by stimulation of the cervical spinal cord, an increased flow of lymph is not observed, and Emminghaus found no increase in lymph-flow from the hind limb of a dog after section of the sciatic nerve. Yet in both these cases the increased vascularity of the part was very manifest, and removal of the peripheral resistance locally must have raised the capillary pressure in the limbs.

This physical view of lymph-formation—modified to some degree by various conceptions introduced from pathology, to which reference will be made later—was held almost if not quite universally until Tigerstedt and Santesson in 1885 and Heidenhain in 1891 brought forward experiments which they considered were incompatible with Ludwig's mechanical explanation.

(ii.) **Heidenhain's Experiments.** — Heidenhain's experiments were of two kinds. In one series he altered the pressure relations in the blood-vessels, in the other he injected so-called "lymphagogues" into the blood-stream. Further, he introduced a change in the method of investigation adopted by earlier workers on the subject, in that he considered the lymph-flow from the thoracic duct and not the lymph-flow from lymphatic vessels in the limbs, as most of his predecessors had done.

That under some conditions increased pressure in the blood-vessels leads to increased lymph-flow, Heidenhain considers as certain. When the portal vein is ligatured, for example, the increased amount of more watery lymph that is obtained from the thoracic duct is, according to him, produced in a strictly mechanical fashion; the capillary pressure in the abdominal area is raised to a maximum, because there is a free access but no outlet for the blood. But Heidenhain found that if the aorta be obstructed above the diaphragm, though the arterial blood-pressure, as registered by a manometer in connection with the femoral artery, had sunk almost to zero, very little change occurred in the amount of lymph obtained from the thoracic duct, and, indeed, sometimes it was actually increased. Moreover, artificial obstruction of the inferior vena cava immediately above the diaphragm caused a very large increase in the amount of lymph-flow, and the lymph obtained differed from the ordinary lymph of venous obstruction in being more concentrated instead of being less concentrated than normal. Thus he found that the lymph, of which 3 c.c. containing 4·8 per cent. of solids was obtained in ten minutes before obstruction, after obstruction of the inferior vena cava, rose in amount to 25 c.c. in ten minutes, and contained 6·6 per cent. of solids. At the same time, as the lymph-flow was increased, the arterial blood-pressure fell from 125 to 37 mm. of mercury.

In his experiments with lymphagogues, Heidenhain divided these substances into two classes: the first comprised such substances as peptone, leech extract, cray-fish extract, mussel extract, and produce a very great outflow of concentrated lymph when injected in very small quantities into the circulation; the second class comprised crystalloids such as glucose, sodium chloride, etc., which, when injected in solution into the blood, lead to an increased outflow of more watery lymph.

In the case of both of these classes of lymphagogue, if care be taken, injection into the circulation may be carried out without the occurrence of any alteration in the arterial blood-pressure. The first class, according to Heidenhain, acts specifically upon the endothelial cells of the capillaries, causing them to secrete an increased amount of a fluid more concentrated than the blood-plasma. Lymphagogues of the second class, he considers, produce an increased flow of more watery lymph, because, when the molecules of crystalloid reach the capillaries, they are excreted by the endothelial cells into the lymph spaces, and there by osmosis lead to a flow of water from the tissue cells into the lymphatic spaces.

(iii.) **Starling's Experiments.**—Though the accuracy of Heidenhain's observations is allowed on all hands, his interpretation of his results has met, in certain quarters, with considerable opposition. In particular, Starling maintains that Heidenhain's experiments are explicable on the assumption that lymph-formation is an expression of two factors, capillary pressure and permeability of the vessel wall. Along with Bayliss, Starling pointed out the important fact that, in the case of the abdominal viscera especially, it is impossible to arrive at any conclusions concerning capillary pressures from consideration of arterial pressures. For the determination of capillary pressures, since direct measurement is out of the question, we must rely on information derived from the blood-pressure in the veins. Heidenhain's observations on blood-pressure were derived from arteries, and Starling, therefore, was unable to accept his conclusion that, when the blood-pressure in the femoral artery was reduced to zero by obstruction of the aorta above the diaphragm, the capillary blood-pressure in the lymph-forming tissues was also reduced to zero. Directly, as well as by a process of exclusion, he proved that the whole increase of lymph, which is seen on obstruction of the vena cava inferior above the diaphragm, comes from the liver, and that the liver is also responsible for the persistence of lymph-flow seen after obstruction of the aorta above the diaphragm. But he and Bayliss had previously shown that obstruction of the vena cava inferior above the diaphragm leads to a great increase of pressure both in the vena cava and in the portal vein, and to a slowing of the circulation through the liver. Under these conditions the liver capillaries are filled with blood under an increased pressure, and this, combined with the diminished velocity of the circulation through the liver, is, in Starling's opinion, sufficient to account for the increased flow of more concentrated lymph from the thoracic duct which undoubtedly obtains. Obstruction of the aorta, again, was found to produce only a moderate fall of pressure in the portal vein, and no fall at all, or a slight rise, in the blood-pressure in the vena cava inferior, though, of course, it leads to an enormous fall in arterial pressure in the vessels coming off from the aorta below the seat of obstruction. In both kinds of experiment, therefore, Starling holds that the difference between intra- and extra-capillary pressure is the cause of the lymph-flow. The greater percentage of solids in the lymph that is obtained both when the vena cava inferior and when the aorta is obstructed above the diaphragm, Starling refers to the greater admixture of hepatic lymph, which he finds normally contains a larger amount of solids than lymph from any other part.

With regard to the action of lymphagogues, Starling also joins issue with Heidenhain. Lymphagogues of the first class, he maintains, act by increasing the permeability of the vessel walls, especially in the liver, whereby the normal or a slightly raised blood-pressure leads to a far greater output of a lymph that is more concentrated than normal. The change in the liver capillaries, which results after injection of these animal substances into the circulation, he approximates to the increase of permeability, which, as will be said later, was regarded by Cohnheim as accountable for the increased exudation which occurs in parts that are inflamed. Lymphagogues of the second class, according to Starling's view, act by producing a condition of hydræmic plethora in which the capillary pressure is greatly raised. The hydræmic plethora which occurs on introduction of a solution of glucose into the circulation had already been investigated by von Brasol, who had shown by hæmoglobinometry that the volume of the circulating blood may after such an intra-vascular injection of glucose be doubled or even trebled. Starling considers that the process whereby this hydræmic plethora is produced on intra-vascular injection of members of Heidenhain's second class of lymphagogues is osmosis. He differs from Heidenhain in that he holds that the osmotic process takes place into the blood-vessels while the molecules of crystalloid are yet within them, whereas Heidenhain holds that it does not take place until the endothelial cells of the capillaries have actively excreted the molecules into the lymphatic spaces. Starling, therefore, believes that there is no need to assume that the capillary walls act in any other way than as physical membranes.

(iv.) **Hamburger's Experiments.**—Besides Heidenhain and Starling, other investigators have entered into the controversy. Hamburger investigated the lymph which flowed from the cervical lymphatic of a horse. He found that the osmotic pressure of the lymph was greater than the osmotic pressure of the serum of blood taken from the jugular vein (*i.e.*, the lymph contained more crystalloid), and that, the horse's head being kept at rest throughout, when the animal was made to walk, the amount of lymph obtained from the cervical lymphatic was 3–5 times as great as when the animal was at rest, though at the same time the carotid pressure sank. From these and from other results he concludes that lymph-formation cannot be due to filtration, but is a secretory process, and that under normal conditions the metabolic products of the tissues are the stimulus which excites the endothelial cells of the capillaries to activity. Cohnstein, who strongly adheres to the mechanical theory of lymph-formation, attacked certain conclusions drawn by Heidenhain from quantitative analyses of blood-serum and lymph, and was in his turn attacked by Mendel. Hamburger's results, too, have not escaped criticism, for Starling and Leathes in particular have raised objections to his conclusions.

From the foregoing remarks it is clear that the apparently simple problem as to the manner in which fluid leaves the blood-vessels and lymph is formed, is far from being settled.

(v.) **The Author's Experiments.**—The author believes that filtration and osmosis, as they are understood at the present day, are not sufficient to account for lymph-formation; indeed, his experiments make it difficult for him to understand how osmosis can play any part in the process at all. The experiments to which reference will be made are concerned with the increased lymph-formation that occurs after intra-vascular injection of sodium chloride, glucose, and urea, members of Heidenhain's second class of lymphagogues. Before they are considered, however, certain physical points must be discussed.

When applying the laws of osmosis to physiological and pathological problems, care must be taken that the essential conditions are similar to those under which the physicist worked when determining those laws of osmosis. The importance of this point is self-obvious, and yet in practice it has been completely ignored.

The laws of osmosis have been determined by physicists for crystalloids dissolved in distilled water, but pure watery solutions—except, perhaps, urine, tears, bile, and sweat—are completely unknown in the animal body. All animal fluids contain proteid, and before the physical laws of osmosis, true for solutions in distilled water, can be applied to physiological and pathological processes, such as lymph- and œdema-formation, it must be shown that those laws are true for solutions of crystalloids in water which contains a certain amount of proteid matter.

But further, the laws of osmosis, as determined by the physicist, have reference to the point at which osmosis ceases.

"the final osmotic pressure." "Indifferent crystalloid substances in equimolecular solution have the same *final osmotic pressure*," "solutions of crystalloids which have the same freezing point have the same *final osmotic pressure*." But when it is considered how great is the final osmotic pressure, it is clear that only when the solutions are extremely dilute can the final osmotic pressure be reached in the animal body. A ·1 per cent. solution of sodium chloride has a final osmotic pressure of about 580 mm. of mercury, an amount approximately four times the pressure in the aorta of a large dog, and probably three or four times the aortic blood-pressure in man. It is impossible to believe that such pressures could be borne by cell membranes or capillary walls, and yet variations in the amount of sodium chloride present in the body naturally, or artificially introduced during experiment, may easily equal or exceed ·1 per cent. If osmosis occurs in the animal body, therefore, it must proceed at pressures far below the final osmotic pressure; at pressures, indeed, which are but slightly greater than the atmospheric pressure. It is the *rate at which osmosis takes place* and not the pressure at which it *ceases* that is, in my opinion, the all-important consideration from a biological point of view.

Now the law that indifferent crystalloids in equimolecular solution have the same final osmotic pressure is only concerned with the pressure at which osmosis comes to a standstill. Concerning the length of time that elapses before the final osmotic pressure is reached, *i.e.*, concerning the rate at which osmosis proceeds, in the case of different crystalloids, it has nothing to say. It is true, for example, that decinormal solutions of glucose and urea have a final osmotic pressure of approximately 2·5 atmospheres, and though *a priori* one would imagine that such solutions should reach their final osmotic pressure in the same length of time, *i.e.*, that osmosis at any given moment should proceed in both solutions at the same rate, this is an unjustifiable assumption in the absence of direct experiment. Moreover, chemists and physicists who have worked on the subject of final osmotic pressures readily admit that, in the case of different crystalloids in isotonic solution, the time which elapses before the final osmotic pressure is reached is very different. But since it is the rate of osmosis, and especially the rate of osmosis at pressures not far removed from atmospheric pressure, and *not* the final osmotic pressure that is of importance in considering the possible effect of osmotic processes in the animal body, it is only if the laws of osmosis that apply to the final osmotic pressure apply also to the rate of osmosis that those laws can be used to explain biological processes. Practically, the rate at which osmosis takes place before any additional pressure is produced —the initial rate of osmosis—is the one which can most readily be determined, and it is to the initial rates of osmosis of such substances as sodium chloride, glucose, and urea, and to the effect of the presence of proteid in the solutions upon those initial rates of osmosis, that attention must be turned for a short time.

It is impossible to refer here to the methods adopted, or to the actual experiments in detail, but the results obtained were very clear. They showed that the final osmotic pressure gives no information whatever concerning the initial rate of osmosis, even when the membrane used is copper ferrocyanide, and that when the membrane used is prepared peritoneal membrane of calf, which presumably bears a closer resemblance to a living animal membrane than copper ferrocyanide, the absence of correlation is even more marked. Thus it was found, when using prepared peritoneal membrane of calf and decinormal watery solutions of sodium chloride, glucose, and urea, that the initial rate of osmosis with glucose is greater than that with sodium chloride, and the initial rate of osmosis with sodium chloride greater than that with urea. And this, though determinations of the freezing point showed that the final osmotic pressure of the glucose and the urea solutions was the same, and the final osmotic pressure of the sodium chloride solution was approximately double that of either of them.

A very clear demonstration of the insufficiency of determinations of the final osmotic pressure, for deciding whether osmosis can or cannot take place at atmospheric pressure between two solutions of different composition on either side of a membrane, is readily given. It has been commonly assumed that osmosis cannot take place between two "isotonic" solutions, *i.e.*, two solutions having the same final osmotic pressure. Further, it has been assumed that if two solutions, not isotonic, are placed on either side of a membrane, osmotic flow will take place from the "hypotonic" to the "hypertonic" solution. Now decinormal sodium chloride solution, since it has a lower freezing point than decinormal glucose solution, is "hypertonic" as regards decinormal glucose solution, and, following the commonly accepted belief, if decinormal glucose solution be separated by a membrane from decinormal sodium chloride solution, the osmotic flow should be *from* the glucose solution *to* the sodium chloride solution. But if the statement made above be correct, that with a peritoneal membrane and decinormal solutions, the initial rate of osmosis with glucose is greater than that with sodium chloride, it follows that at atmospheric pressure, the osmotic flow should be in exactly the reverse direction to that which consideration of the final osmotic pressures would lead us to suppose. That, in other words, assumptions made from consideration of the final osmotic pressure would not be borne out by fact at a time when osmosis was taking place with the utmost ease. It can be shown by actual experiment that this is the case, and that at atmospheric pressure, water passes by osmosis from the so-called "hypertonic" sodium chloride solution to the so-called "hypotonic" glucose solution. In the same way the idea that osmosis cannot occur between the so-called "isotonic" decinormal solutions of urea and glucose is not borne out by experiment, for at atmospheric pressure, and using a prepared peritoneal membrane, osmosis readily takes place from the urea solution to the glucose solution.

The explanation of these results, even if a satisfactory explanation had been given, does not concern us here. The lesson they teach is that, at pressures which are within reasonable limits of possibility for the animal body, conclusions as to the occurrence or non-occurrence of osmosis, drawn from determinations of the final osmotic pressure, or what amounts to the same thing, from the freezing point, are utterly fallacious.

But even if we have come to the conclusion that in animal experiments with reference to osmosis we must substitute initial rates of osmosis for final osmotic pressures, there remains the question whether the presence of proteid material in the solution has an effect or is without effect upon osmosis. This point has been investigated by the author in three different series of experiments.

In the first series, distilled water to which 1 c.c. per litre of horse's blood-serum had been added, was made to take the place of distilled water throughout.[1] Instead of being dissolved in distilled water, the solid crystalloids were dissolved in this faintly albuminous water; instead of placing distilled water on the other side of the membrane, faintly albuminous water was placed on the other side of the membrane. In the second series, unaltered ox blood-serum was used as the solvent for the crystalloids and as the fluid on the other side of the membrane. In the third series, unaltered blood-serum of oxen, horses, and sheep were placed on one side of the membrane, and on the other were placed watery solutions of sodium chloride in different degrees of concentration. Each of these series must be considered separately.

In the first series, where the conditions were identical with those obtaining in the experiments that have previously been described, excepting that faintly albuminous water took the place of distilled water, it was found that the initial rates of osmosis of the crystalloids, though they bore the same ratios to one another, were greatly reduced. The initial rate of osmosis with glucose was still greater than that with sodium chloride, the initial rate of osmosis with sodium chloride still greater than that with urea, but the values obtained were less by about one-third than those obtained with distilled water, and in the absence of even this minute trace of proteid. Proteid material, therefore, even if present only in traces, greatly impedes osmosis. This is the more important, in that the amount of proteid added was insufficient to produce any alteration in freezing point of the solutions, and was not recognisable by any of the ordinary tests, though the precipitation of globulins in the distilled water led to a slight haziness of the fluid when seen in bulk.

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[1] This faintly albuminous water contained about ·0075 per cent. of proteid, for of course the greater proportion of the added horse serum was water alone.

In the second series, where highly albuminous fluid was used as the solvent and as the fluid on the other side of the membrane, the initial rate of osmosis was further reduced. The marked diminution in initial rate of osmosis that occurs with faintly albuminous solutions would naturally lead one to expect that, when the amount of proteid present is so great as it is when unmodified serum is used, osmosis should not occur at all. With urea this was found to be the case even over a prolonged period, but with glucose and with sodium chloride, osmosis occurred, though the initial rates of osmosis were less than half the initial rates obtained when distilled water was used as solvent and as fluid on the other side of the membrane.

In the third series of experiments, which was carried out at 37° C., it was found that the strength of sodium chloride solution, which it is necessary to place on the other side of the membrane before osmotic equilibrium is produced, is—speaking generally—1·6 per cent., in spite of the fact that the tonicity of the serum, as determined by Hamburger's method and by the freezing-point method, gives a value of about ·95 per cent. sodium chloride as the isotonic strength. It was further found that the greater the amount of proteid in the albuminous solution (the crystalloids being taken as constant) the more concentrated must be the sodium chloride solution on the other side of the membrane which shall be in osmotic equilibrium with it.

From all these experiments, three points stand clearly forward: (1) it is impossible, from considerations of the final osmotic pressure or of the freezing points of crystalloids in equimolecular solution, to make deductions concerning the initial rates of osmosis of those crystalloids; (2) osmosis is impeded by the presence of proteid material in the fluids; (3) the greater the amount of proteid in a crystalloid solution the greater must be the concentration of a watery solution of sodium chloride on the other side of the membrane necessary to produce osmotic equilibrium at atmospheric pressure. An important point shown by the experiments, which does not concern us here, but to which reference will be made when discussing absorption, is that dialysis is impeded to a far less extent by the presence of proteid in the solutions than is osmosis.

The author's animal experiments in connection with lymph-formation were chiefly directed towards the following questions. 1. On intra-vascular injection of such quantities of sodium chloride, glucose, and urea, severally, as bring the amounts of those substances in the blood up to the point at which the blood theoretically becomes a decinormal (blood) solution of the crystalloid injected, do the amounts of lymph-flow obtained from the thoracic duct bear the same ratios to one another as are borne by the initial rates of osmosis of those substances to one another? That is to say, is the amount of lymph-flow after intra-vascular injection of glucose greater than that after intra-vascular injection of sodium chloride, the amount of lymph-flow after intra-vascular injection of sodium chloride greater than that after intra-vascular injection of urea? If this be so, there is reason to conclude that the capillary wall is a physical membrane similar to prepared peritoneal membrane of calf.[1]

It was found that such a correspondence does not obtain. After intra-vascular injection of sodium chloride the amount of lymph-flow is greater than after injection of glucose, whereas the initial rate of osmosis with sodium chloride is less than the initial rate of osmosis with glucose. Urea maintains the lowest position, both as far as concerns its initial rate of osmosis and the increased amount of lymph-flow which its intra-vascular injection calls forth. It was further found (and this point is very important), that in the same animal, when the amount of water present in the tissues and available for osmosis has been diminished by loss of lymph, etc., injection of a crystalloid with a lower initial rate of osmosis (urea) may lead to a greater increase in the amount of lymph-flow than that to which injection of an equal[1] amount of another crystalloid with a higher initial rate of osmosis (glucose) has led, when the amount of water present in the tissues and available for osmosis had not been diminished by loss of lymph, etc.

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[1] If such ratios are not found it does not follow that the capillary wall is not a physical membrane, for Graham and Lothar Meyer both pointed out that osmosis is greatly affected by the nature of the membrane, even though it always be a dead membrane; it only follows that the capillary wall is a membrane not comparable with prepared peritoneal membrane of calf.

2. Is intra-vascular injection of a crystalloid in solution followed by a temporary diminution in the amount of lymph-flow from the thoracic duct? If, on intra-vascular injection of a crystalloid, water enters the blood-vessels by osmosis, the first water that enters must be derived from the lymphatic spaces which immediately surround the capillaries. Since these spaces are in direct connection with the lymphatic vessels and the thoracic duct, the first effect of such intra-vascular injection of crystalloid must be a diminution in the amount of lymph-flow from the thoracic duct: the lymph, instead of passing out by the thoracic duct, passes directly into the blood-vessels.

The importance of this question had not escaped the notice of Heidenhain, who states that he never found a diminution but always an acceleration of the lymph-flow from the very first. Cohnstein, on the other hand, found a preliminary and marked diminution in the lymph-flow from the thoracic duct on intra-vascular injection of a crystalloid. The author made thirty-one investigations upon this point, of which twenty-two were in favour of Heidenhain, nine in favour of Cohnstein.

3. If the increase in amount of lymph-flow be due to increased filtration, the changes in venous blood-pressure which result from intra-vascular injection of a crystalloid, and which are an indication of the changes in capillary blood-pressure, must be identical in direction with the changes given by the lymph-flow. Is output of lymph greatest when venous pressure is highest? Does the output of lymph return

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[1] *I.e.*, molecularly; the percentage composition of the glucose solution (mol. wt. of glucose = 180) was of course exactly three times the percentage composition of the urea solution (mol. wt. of urea = 60). The volume of solution injected into the circulation in all the experiments was one-four hundredth of the body weight of the animal; the object of this was to introduce as little as possible beyond the crystalloid, and in any case to inject comparable quantities throughout.

to the normal level when the venous pressure returns to normal?

It was found[1] that the maximum pressure in the inferior vena cava occurs within two minutes of the end of injection of the crystalloid, whereas the maximum flow of lymph from the thoracic duct is not obtained until about ten minutes have elapsed; and that, further, the output of lymph from the thoracic duct is greater than normal, frequently for half an hour after the pressure in the inferior vena cava has again fallen to normal or even fallen below normal.

Two additional difficulties in the way of accepting a purely physical explanation of lymph-formation must also be mentioned. When a large quantity of normal saline solution is injected into the circulation, the specific gravity of the blood falls, but rapidly rises again, and does not cease to rise until it has reached a *higher level* than obtained previous to the injection. At this moment the blood contains a smaller percentage of water than it did before injection, and it can be shown that the actual volume of the plasma has diminished. It follows from this, that more fluid has left the blood-vessels than was introduced with the intra-vascular injection, and it is extremely difficult, if not impossible, to understand how this can occur if we are limited to filtration and osmosis in our explanation of the process. It is useless to suggest that the permeability of the vessel wall is increased,[2] for the phenomenon is only seen after the first, or first and second, injections of a series. If it be assumed that in these injections the permeability of the vessel wall is increased, it must be assumed in the case of later injections of the series where the phenomenon is absent, and where the capillary pressure, as shown by the venous pressure, is also raised, that the permeability of the vessel wall returns to normal or even becomes diminished.

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[1] My results, though not my conclusions, in this respect agree with those of Starling.

[2] I have never been able to grasp the adequacy of any explanation of either lymph- or œdema-formation which appeals to alterations in the "permeability" of the vessel wall. The only test which we possess for showing that a capillary wall is more "permeable" than normal, is the fact that the amount of lymph-flow is increased while the lymph contains a greater percentage of solids. To explain an observed increase in the amount and concentration of the lymph by an increased "permeability" of the capillary wall is therefore to reason in a circle. But more than this, such an attempted explanation only obscures the matter. In the case of a *dead* membrane, variations in permeability are due to physical conditions as opposed to vital conditions, and variations in the amount of fluid which passes through the membrane may rightly, *cæteris paribus*, be taken as a test of variations in permeability, though of course they give no indication as to the physical changes which take place in the membrane. But in the case of a *living* membrane the test fails completely, in that variations in the amount of fluid which

The other difficulty has especial reference to the part played by osmosis in lymph-formation. It has been said that the greater the amount of proteid in the solution (blood-serum), the more concentrated must be the sodium chloride solution on the other side of the membrane in a physical apparatus, which shall be in osmotic equilibrium with it at 37° C. and at atmospheric pressure. It follows, since lymph contains less proteid than blood, that it is in osmotic equilibrium, under the conditions given, with a more dilute solution of sodium chloride than is the blood whence the lymph is formed. Now, if a weak solution of sodium chloride is placed on one side of a membrane, and a strong solution of sodium chloride is placed on the other, the osmotic flow is from the weak towards the strong solution, and hence experiments on an artificial scheme would seem to indicate that if osmosis occurred in the animal body, its only effect would be to withdraw water from the body generally into the blood-vessels so long as the blood continued to be a more highly albuminous fluid than the lymph.

passes through the membrane may either be evidence of an increased permeability in the physical sense, or evidence of the greater exercise by a living tissue of its specific function, or evidence of both. The dead capillary wall undoubtedly allows more fluid to pass through it than the living capillary wall, but secretion—a process which in its essential conception is bound up with life—is impossible, and, therefore, if lymph- and œdema-formation were associated with *dead* capillary walls, no obscurity would be introduced by use of the term "permeable." But lymph- and œdema-formation occur when the capillary wall is living, and the processes may be either such as one could imitate with a dead membrane or be such as one could under no known condition imitate with a dead membrane. Consequently, any theory which attempts to *explain* increased lymph-formation or œdema-formation by an increased permeability of the capillary walls does not do so, but simply re-states in other words the already known fact that more fluid passes out of the blood-vessels It leaves the question as to whether the increased transudation is a physical or is a vital process completely untouched, or rather, since "permeability" is a physical term, it tacitly assumes the very point at issue.

But though the author's experiments lead him to believe that lymph is formed by a secretory process, it is necessary, before leaving the subject, to mention that he has met with facts capable of a purely physical explanation. Thus, after intra-vascular injection of sodium chloride, glucose, and urea, the falls in specific gravity of the blood and the relative increases of lymph-flow vary directly with the initial rates of osmosis of the three crystalloids *through a copper-ferrocyanide membrane*; so also the relative increase of lymph-flow in different animals after intra-vascular injection of weak saline solution in amounts bearing a constant ratio to the body weight, is approximately a constant.

V. **Œdema - formation. — (i.) Clinical Varieties of Œdema.**—If the subject of œdema-formation has derived many of its arguments from investigations made on lymph-formation, the converse is none the less true, for, long before Ludwig and his pupils performed experiments with reference to lymph-formation, Richard Lower investigated experimentally certain forms of œdema.

Etymologically, the very name "dropsy," by which œdema is frequently known, is evidence of its early clinical recognition, and, as a matter of fact, it was described by Hippocrates in the fifth century B.C. Clinically, the varieties of œdema are divided according to the conditions under which œdema shows itself. Thus there is "cardiac" œdema, "renal" œdema, "inflammatory" œdema, "cachectic" œdema, "chlorotic" œdema, and so on.

(*a*) *The Œdema of Passive Congestion.*—Frequently those forms of œdema in which the clinical condition is associated with increased venous pressure are included under the one name of "passive" œdema. Examples of this so-called passive œdema or dropsy are seen in the œdematous condition of the subcutaneous tissues, and the collections of fluid in the pleural (hydro-thorax), pericardial (hydro-pericardium), and peritoneal (ascites, hydro-peritoneum) cavities found in the later stages of cardiac disease; in the ascites which occurs when obstruction to the flow of blood in the portal veins is introduced by cirrhosis of the liver; in the œdema of the hand or finger occurring as the result of venous obstruction, produced by a tight surgical bandage or a tight ring. The characteristic points about these forms of œdema are that the œdema fluid exudes from the capillaries and the small veins on the distal side of the cause of venous obstruction, and that it shows itself first where the pressure is greatest. Thus, in the case of cardiac disease, the first signs of œdema are seen about the ankles, where such venous obstruction as is due to the central lesion is aided to the greatest extent by the effect of gravity.

(*b*) *Inflammatory Œdema.*—Inflammatory œdema occurs in the neighbourhood of a focus of inflammation, and from many points of view it would be more convenient to discuss its pathology in the following chapter, but on the whole it seems better to discuss it along with the exudations generally. In its distribution it is localised, and in this respect it resembles the œdema of passive congestion; but, as will be shown immediately, in respect of its chemical composition and of some of its properties, it differs greatly from the œdema of passive congestion.

(*c*) *Renal Œdema.*—The œdema which is seen in renal disease is of two kinds. One variety is proper to renal disease itself and is met with in acute nephritis. It is a general, soft œdema, and is characterised by the facts that its distribution seems to be independent of gravity, and that it shows itself first where the tissues are most lax. Thus it is earliest seen in the loose tissue of the eyelids. There can be no doubt that the dropsy described by Hippocrates was of this nature. The other variety of renal œdema is, strictly speaking, not renal at all, but cardiac. It shows the characteristic distribution of cardiac œdema, and, as in the case of every œdema that is associated with venous obstruction, considerable pressure must be exerted by the finger before "pitting" is seen. It accompanies not acute but chronic renal disease. The *rationale* of its causation certainly is that the hypertrophy of the left ventricle, which commonly occurs along with chronic interstitial nephritis, commences to fail. Consistently with this explanation, it is found that this variety of œdema is associated with other signs of cardiac failure, such as the appearance of valvular murmurs, pulsation of the veins in the neck, cyanosis, etc.

(*d*) *Œdema of Cachexia.*—Cachectic œdema is usually far less marked than either cardiac or renal œdema. It is often limited to the appearance of a small amount of swelling in the neighbourhood of the ankles. It may occur under almost any condition in which the health of the patient is severely broken, and is generally associated with pronounced anæmia.

(*e*) *Chlorotic Œdema.*—Chlorotic œdema is a somewhat misleading term. There is no doubt that chlorosis is often associated with the presence of small amounts of œdema about the ankles, and the general doughiness of the skin and subcutaneous tissue which is commonly seen in chlorosis, is probably in part of the nature of an œdema. But it is only because chlorosis is the most common variety of anæmia, and not because of any special peculiarity in chlorosis itself that the name chlorotic œdema is justifiable. For œdema may be present in all forms of anæmia, provided that they are severe and of some standing. There is one point, however, which is worthy of mention, and it is that in many cases of chlorosis, as shown independently by A. E. Garrod and by Dickinson, the pulse suggests that a renal element is present in the condition. It is therefore possible that in such cases the œdema is of a mixed anæmic and renal nature.

(ii.) **Composition of Œdema Fluids.**—The composition of dropsical fluid, speaking generally, is the same as that of blood-plasma, excepting that it is more dilute. Instead of containing about 91 per cent. of water as does blood-serum, dropsical fluids contain 96 per cent. or more. The essential difference between the two fluids consists in the relative amounts of proteid which they contain, for the amount of salts in both is approximately the same. In this respect dropsical fluids resemble lymph. Nevertheless, in all dropsical fluids there is a far greater amount of proteid than in ordinary lymph, and even in those cases where the fluid contains the least amount of proteid, there is usually enough present to convert the fluid into a solid mass on boiling.

The composition of dropsical fluids, however, varies in the different forms of œdema. Thus the fluid which exudes in parts that are the subject of venous congestion is of a lower specific gravity and contains less proteid than fluid which is poured out during an inflammatory process. In the former case the specific gravity will be perhaps 1008, in the latter 1018. Moreover, the composition of dropsical fluids varies according to the situations in which they are found when they are induced by one and the same general disease. They may be arranged in the following order according to their richness in proteid: (1) pleuritic fluid; (2) peritoneal fluid; (3) cerebro-spinal fluid; (4) fluid of subcutaneous œdema. This is well shown in the following table:—

*Composition of various dropsical fluids removed simultaneously from the body of a person who had died of albuminuria (C. Schmidt).*

| | Fluid from | | | |
|---|---|---|---|---|
| | Pleural Cavity. | Peritoneal Cavity. | Subarachnoid Space. | Œdematous Connective Tissue of Extremities. |
| Water in 1000 parts, | 963·95 | 978·91 | 983·54 | 988·70 |
| Solid matter ,, ,, | 36·05 | 21·09 | 16·46 | 11·30 |
| Organic ,, ,, ,, | 28·50 | 11·32 | 7·98 | 3·60 |
| Inorganic ,, ,, ,, | 7·55 | 9·77 | 8·48 | 7·70 |

Dropsical fluid removed at different times from the same sac shows a remarkable constancy in composition. Hoppe-Seyler gives the following analyses of the fluid removed by paracentesis from the peritoneal cavity in a case of cirrhosis of the liver.

| | First Paracentesis. | Second Paracentesis. | Removed after Death. |
|---|---|---|---|
| Water in 1000 parts, | 984·50 | 982·53 | 983·33 |
| Solid matter ,, ,, | 15·50 | 17·47 | 16·67 |
| Inorganic salts ,, ,, | 8·46 | 8·13 | 8·24 |
| Albumin ,, ,, | 6·17 | 7·73 | 6·11 |

The volume of fluid which collects in one of the serous cavities is, of course, to some degree limited by the normal capacity of that cavity. In the case of the peritoneal sac the amount of fluid may vary from a few cubic centimetres to several litres: those cases in which a large amount of fluid is present are generally accompanied by severe symptoms due to the pressure under which the fluid is pent. Not infrequently in the abdominal cavity ascitic fluid may exert a pressure of 25–30 millimetres of mercury. Subcutaneous œdema also varies considerably in amount: sometimes it is barely perceptible, at other times the circumference of the part, if it be a limb, may be nearly doubled, and the natural depressions are completely lost. Pitting on pressure, which is characteristic of subcutaneous œdema, is of course more or less evident according to the greater or the less amount of fluid that has collected in the subcutaneous tissue. When œdema is associated with increased venous pressure, the tension of the fluid in the subcutaneous tissues is greater than when it is associated with acute renal disease, and hence in the former case the œdema is spoken of as "hard," in the latter case as "soft."

In the matter of spontaneous coagulation, a broad distinction may be drawn between exudations from the blood-vessels. In the passive dropsies, where the endothelium of the surface is normally intact when the effusion takes place into a serous cavity, and where the number of leucocytes present in the effusion is very small, coagulation rarely takes place. On the other hand, inflammatory effusions in which many leucocytes are usually present are far more likely to coagulate. Nevertheless, there are many exceptions to the above statements. In ascites, it is not uncommon to find flakes of fibrin present, and not all inflammatory effusions coagulate—for example, the fluid obtained from cutaneous blisters rarely coagulates. The explanation of this variability, so far as concerns coagulation, is difficult. In some cases, no doubt, the presence or absence of leucocytes makes a difference, but this is not so in all. It is by no means uncommon to find inflammatory exudations rich in leucocytes which do not coagulate (*e.g.*, pus); in some of these cases we may, perhaps, assume that the explanation lies in the presence of a substance (? albumoses) which inhibits coagulation.

For some unknown reason, inflammatory exudations that are associated with the presence of the pneumococcus show a marked tendency to coagulate, and it is in great part on this account that fibrinous exudations are so common in the pleural cavities.

(iii.) **The Pathology of Œdema.**—(*a*) *Older Views and Experimental Evidence.*—It has already been said that Richard Lower in 1680 ligatured the inferior vena cava in animals, and obtained œdema of both hind limbs. From this experiment he came to the conclusion that the œdema of the lower extremities which occurs in heart disease, where there is obstruction to the flow of blood in the inferior vena cava, depends upon an increase of pressure in the veins, which is transmitted backwards and leads to an exudation from the smaller vessels. Though this view was not universally accepted by Lower's contemporaries, it nevertheless held its own for two centuries without serious experimental question. It was strongly supported by Bouillard in 1823, and amplified by Andral in 1829. Andral showed that the obliteration of many veins is necessary for the production of œdema, since the free anastomosis of the veins readily allows the passage of blood to the heart, after obliteration of one—even though that be the main—trunk of the limb. But in 1869 Ranvier repeated Lower's experiments without success. He afterwards modified them by adding to ligature of the vena cava, section of the sciatic nerve on one side. On this side œdema appeared, while the limb in which the sciatic nerve was intact remained free. The first evidence of œdema was visible around the *tendo Achillis* and came on about an hour after section of the nerve. Ranvier ascribed the œdema which he obtained to the removal of vascular control by the vaso-motor nerves, and regarded the experiments as evidence that vaso-motor nerves normally control the output of fluid from the blood-vessels.[1] Bouillard, who was present at the reading of Ranvier's paper before the French Academy, regarded this as another variety of œdema, but in no way as contradicting the occurrence of passive œdema from obliteration of veins which he had "himself produced experimentally in several cases, and had seen clinically produced hundreds of times." Cohnheim regarded the cardiac or passive variety of œdema as "the result of two pressures, venous obstruction and arterial pressure, which, acting against one another, cause an outpouring of fluid through the walls of the thinnest vessels, the capillaries, and probably also the smallest veins." Ranvier's results, he considered, did not show the importance of the vaso-motor nerves as their author insisted, but he explained the œdema by pointing out that "the congestion resulting from section of the nerve very unfavourably modifies the inequality between inflow and outflow." As a result of Cohnheim's criticism, Ranvier somewhat altered his position, and in 1881 he and Cornil wrote: "If in an animal in which one has tied a vein, the vaso-motor nerves be cut, the arteries being dilated, a larger amount of blood reaches the part, and the tension becomes sufficient to lead to transudation of serum. This increased tension is the true cause of dropsy: if this tension be sufficient independently of obliteration of the veins, œdema will occur. All kinds of œdema, except, perhaps, the œdema of cachexia, may be referred to the same cause." In 1889, Wooldridge described the following important experiment. "If a solution of tissue-fibrinogen obtained from the thymus gland be injected into the circulation through the jugular vein, and the femoral vein be then ligatured, the effect is most pronounced and is as follows: either the most extensive and rapidly developing simple œdema of the leg occurs, or an enormous hæmorrhage 'per diapedesin' takes place throughout the tissues of the limb; or the two are combined—there is hæmorrhage and œdema."

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[1] In spite of many attempts to connect lymph-formation with nerve action, the existence of lymph-secretory nerves has never been demonstrated.

All these experiments obviously bear upon the passive variety of œdema in particular, and in most cases they explain the œdema upon mechanical principles in which filtration plays the chief part. And at the present day, this variety of œdema is almost universally regarded as being dependent directly upon increased venous and capillary pressure, combined in most cases with deficient removal of the fluid by the lymphatics. Of late years, following in the path of the investigations by physiologists upon lymph-formation, there has been a tendency to call the physical process of osmosis to the aid of filtration, in the explanation of œdema. At the same time, there has also arisen a school of pathologists who find it difficult to explain all the factors of œdema-formation on any known mechanical or physical principles, and who regard œdema as the expression of an increased exercise by the endothelial cells of the blood-vessels of their specific secretory function.

(*b*) *Modern Views, especially those of Cohnheim.*—Cohnheim, by his work on œdema and on inflammation, has largely influenced views on œdema-formation. He taught that œdema essentially depends on one or both of two factors: (1) increased pressure, (2) increased permeability of the vessel wall. In the case of passive œdema, he held that increased pressure is a sufficient explanation of the observed facts, basing his view on the experiments of Emminghaus, who asserted that the lymph-flow from the lymphatics in the hind limb of a dog is increased by increase of venous pressure. Cohnheim says in his *General Pathology* that, "with increased venous pressure, as many cubic centimetres of lymph may be obtained from such a lymphatic in the same time as, previous to the increase of pressure, there were obtained drops." To this point we shall return.

With the exception of the varieties of passive œdema, according to Cohnheim, all forms of œdema depend upon an increased permeability of the vessel wall. It was especially in reference to the inflammatory variety that he elaborated this view, but he held that the same principle applied in many other cases. In particular, he included the so-called cachectic œdema in this group.

The older view of cachectic œdema was, that it depends upon hypalbuminosis or a deficiency of albumen in the blood-plasma. It is certain that a fluid which contains a small quantity of albumen passes through a membrane more readily than a fluid which contains a large quantity of albumen; it is also certain that in most of the cases, if not in all, in which cachectic œdema occurs, the blood contains a smaller proportion of albumen than normal, *i.e.*, it is hydræmic. It was therefore held that cachectic œdema depends upon hydræmia. Cohnheim and Lichtheim investigated the subject experimentally. They showed that hydræmic plethora, produced by injecting saline solution into the circulation, leads to no visible œdema; the only result is that those tissues whose normal function it is to produce a watery secretion (kidney, salivary glands, pancreas, mucous membrane of the gastro-intestinal tract), secrete a larger amount of a very watery fluid. If the amount of saline solution injected be very great (10 per cent. of the body weight or more), these tissues become definitely œdematous, and, in addition, a certain amount of fluid is poured out into the serous cavities of the body, in particular into the peritoneal cavity. Simple hydræmia, as distinguished from hydræmic plethora, was produced by injecting into the circulation an amount of salt solution equal to an amount of blood that had previously been abstracted from the animal, but under these conditions not the slightest trace of œdema was found in any tissue. Moreover, on passing salt solution through the vessels of a rabbit's ear at the normal pressure of the blood, they found that no increase of lymph-flow occurs. They therefore concluded that hydræmia as such is not the cause of cachectic œdema. The different result which obtains after the production of hydræmic plethora, they held, really depends upon the increase of venous pressure, which is produced by the hydræmic plethora.

But Cohnheim and Lichtheim found, on the other hand, that if one paw of a dog is inflamed, injection of two litres of salt solution leads to œdema of that paw and not of the others, and that when a dog, by repeated abstraction of blood and replacement of the blood by salt solution, has been kept hydræmic for days, ligature of the femoral vein leads to the appearance of œdema in the limb, whereas under normal conditions such is not the case. In both of these experiments the vessel walls are modified, and in this fact, according to Cohnheim, lies the whole explanation of cachectic œdema. For "the injured vessel wall is more permeable than normal, and when this is the case the normal or less than the normal blood-pressure is sufficient to produce an increase of lymph-flow, or, in other words, to produce œdema."

Renal dropsy, which by many of the older writers was regarded as due to hydræmic plethora, was held by Cohnheim to be of the same type as inflammatory œdema. In supporting the older view, Bartels had brought forward the clinical fact that in nephritis the amount of dropsy varies inversely with the amount of urine excreted. Besides the experimental evidence which has been given above on the subject of hydræmic plethora, Cohnheim adduced against the old view of renal dropsy the fact that, where there is complete anuria or suppression of urine from impaction of calculi in the ureters or other similar cause, there is an absence of the characteristic œdema of acute nephritis. In such a case, if any, he argued, there must be hydræmic plethora, and yet there is no dropsy.

The actual occurrence or the absence of œdema when an excessive amount of fluid is leaving the blood-vessels, depends upon the ratio of the amount of transudate to the amount flowing away by the lymphatics. If all the transuded fluid is carried away, it follows that œdema, as evidenced by increase in volume of the limb and pitting on pressure, cannot show itself. Hence, any cause which impedes the flow of lymph through the lymphatics can favour the occurrence of œdema. Cohnheim denied that obstruction of lymphatics—even obstruction of the thoracic duct itself—is ever the primary cause of œdema, owing to the freedom of anastomosis of these vessels.[1] In his opinion, whatever other conditions might or might not assist in the process, an increased output of fluid by the blood-vessels must exist, whether that increased output depend upon increased pressure within normal blood-vessels or upon increased permeability of the blood-vessel wall, or upon both of these factors in conjunction. He did not deny that a part might be played by the endothelial cells of the blood-vessels themselves; indeed, he frequently insists in his *Lectures on General Pathology* that the capillaries are living and not dead membranes. Thus he says,[2] "We are not yet in a position to propound a mechanical theory of the œdema of stagnation, and the aid of *unknown influences*

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[1] In this matter Boddaert differs entirely from Cohnheim.

[2] Pp. 515 and 516, New Syd. Soc. translation.

*proceeding from the living wall* must be called in for its interpretation;" and, "the endothelium of a vessel is . . . a *living tissue*, or, if you prefer it, *organ*, with a metabolism which, though quite unknown to us, is certainly very active."

Hamburger departs from the view held by Cohnheim, in that he believes that the passive œdema of venous congestion is not the result of increased pressure in the small veins and capillaries, but is due to an increased lymph-secretion by the capillary endothelium, which is stimulated to that increased secretion by the waste products that accumulate in the blood-vessels as the result of venous obstruction. The "increased permeability" of Cohnheim he regards as evidence that the vessels from injury have, in part or in whole, lost their character as a secreting organ, and have become porous like a filter. He agrees with Heidenhain, that some forms of œdema are due to definite stimulation of the capillary endothelium by lymphagogues, and he regards these substances as being formed during disease.

Starling, consistently with his view of normal lymph-formation, regards œdema-formation as dependent upon physical factors, amongst which increased pressure and increased permeability of the vessel wall are the chief.

(*c*) *The Author's View.*—The author's experimental investigations upon this subject have principally been concerned with the œdema which accompanies passive congestion. Owing to the difficulty of appreciating small changes in the volume of limbs, he has examined (by Roy's method) the specific gravity of the blood and blood-plasma, arterial and venous, the specific gravity of voluntary muscle and of skin, and the amount of lymph-flow from the lymphatics. He found, in the dog, that increase of the blood-pressure in the veins of a hind limb for one hour is not accompanied by any modification in the specific gravity of the blood or blood-plasma, arterial or venous, or in the specific gravity of the voluntary muscle or skin in the body generally (as represented by the *other* hind limb), or in the specific gravity of the arterial blood or blood-plasma, or of the voluntary muscle or skin in the *affected* hind limb. With regard to the lymph-flow in the affected limb, the author differs from Emminghaus, in that he never found that simple increase of venous pressure during the hour that it existed, led to an increase in the amount of lymph-flow. In the affected limb, the specific gravity of the venous blood and of the venous blood-plasma on the distal side of the ligature, is raised during the hour that the ligature is *in situ.* This is only to be expected when one considers that the length of time which a given volume of blood remains in the limb is increased, owing to diminished velocity of blood-flow, and, therefore, that a greater length of time is given for removal of lymph from that volume of blood. The venous pressure in the affected limb in these experiments, as measured by a mercury manometer in connection with the femoral vein, varied between 50 and 75 mm.,[1] the blood-pressure in the carotid being over 100 mm., and hence, though there was great venous obstruction, a circulation through the limb was kept up.

(*a*) *Inadequacy of the Physical Explanations of Passive Œdema.*—Now if the exudation from the veins, which forms œdema in cases of venous congestion, were due to the increased venous pressure alone acting in a physical manner, the increased transudation should show itself immediately on the establishment of increased venous pressure. That is to say, the specific gravity of the muscles and skin in the affected limb should fall, or the amount of lymph-flow should increase; moreover, since any excess of fluid which left the blood-vessels would be derived from the blood of the body at large, the specific gravity of the arterial blood and blood-plasma should rise, or if it remained constant the specific gravity of the tissues in the rest of the body should rise. None of these changes occur during a period of one hour when the obstruction to the venous blood-flow in the limb is enormous, and, therefore, it is quite impossible, in the author's opinion, still to maintain the view that increase of venous pressure is *per se* the cause of the so-called passive œdema. It is beside the mark to call attention to the undoubted fact that such œdema is very manifest "next day" or "after some hours," for it is essential, if the increased exudation depends upon increased filtration, that it should commence to take place without the intervention of any interval. And though it might not be possible to recognise œdema by increase in volume of the limb or by pitting on pressure in the very earliest stage of the œdema, this objection does not hold good with determinations of specific gravity in which variation of half a degree is readily recognised.[1]

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[1] The pressure in the femoral vein of a dog is normally 4–5 mm. of mercury.

But the argument is still further strengthened when it is shown that, with the onset of œdema in a limb, marked changes in specific gravity occur, which affect not only the limb itself but also the body generally.

It is always possible to produce œdema after placing a ligature round the limb of a dog sufficiently tight to completely obstruct all flow of blood through the limb, and maintaining hæmostasis for one hour. During hæmostasis, no changes in specific gravity of blood or of tissues take place in parts other than the affected limb, and here the only changes are that the specific gravity of the venous blood and blood-plasma rises, and the volume of the venous blood-plasma and the amount of lymph-flow are diminished. After removal of the constricting ligature, if the venous pressure in the limb be raised, and that to a much smaller degree (25–30 mm. of mercury) than in the experiments that have previously been mentioned, œdema rapidly comes on, often to so great an extent as to be readily recognisable by pitting on pressure, and important changes in specific gravity are to be noted. The specific gravity of the arterial blood of the whole system rises; the specific gravity of the arterial blood-plasma rises, though sometimes it falls in spite of a rise in the specific gravity of the arterial blood as a whole; the specific gravity of the venous blood and blood-plasma in the affected limb rise, and to a greater extent than when there has been no hæmostasis; the specific gravity of the venous blood of the rest of the body generally rises, but tends to lose its normal superiority over the specific gravity of the arterial blood; the specific gravity of the venous blood-plasma of the rest of the body generally falls; the specific gravity of muscle, and, to a less extent, of skin, in the affected limb fall, but in the rest of the body, as represented by the unaffected limb, they rise.

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[1] In a medium-size fox terrier such a rise in specific gravity of the blood means approximately that 7 c.c. of lymph have been removed from it. In œdema experiments variations of six degrees and more are quite common.

Now the meaning of these changes obviously is that in the affected limb, fluid is leaving the blood-vessels and is becoming collected in the tissues, and that in the unaffected limb (and the rest of the body in all probability), fluid is leaving the tissues and being carried away by the venous blood. Further, after hæmostasis, the amount of lymph-flow obtained from a lymphatic in the affected limb increases as the venous pressure is increased, returns to normal as the venous pressure is allowed to return to normal, whereas this is not the case under ordinary circumstances. By hæmostasis kept up for one hour, the relation between blood, blood-vessels, lymphatics, and tissues has become altered to such a degree, that they react to an increase of venous pressure in a manner utterly unlike that in which they react if hæmostasis has not been produced.

($\beta$) *Importance of the Tissues in Œdema-formation:* (1) *General.* —Leaving consideration of the blood-vessels on one side for the moment, it is plain that during hæmostasis the tissues of the limb are affected in two ways: (1) they are deprived of nutriment; (2) the waste products of their own metabolism are not removed.[1]

Though we are ignorant of the manner in which the tissue cells make known their requirements to the blood-vessels, there is ample evidence that they do so. And more than this, they make known their requirements to the other tissues in far distant parts of the body. This latter point will be left for the present.

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[1] It is astonishing how in all discussions concerning lymph- and œdema-formation the tissues have been left out of consideration, when we remember that every condition which affects the small blood-vessels, and especially the capillaries, must at the same time affect the tissues also. In some cases even, in which œdema occurs, the tissues are affected first and to the greatest extent. Thus when blistering fluid is applied to the skin the many layers of the epidermis must of necessity be exposed to a greater extent to the action of the blistering fluid than the cutaneous blood-vessels: it is only after the epidermis has been affected that these blood-vessels are reached. It is a fault in the mechanical explanation both of lymph- and of œdema-formation that it places the tissues absolutely at the mercy of the vascular system; the amount of lymph which the tissues receive, according to that explanation, does not depend upon the needs of the tissues but upon the condition of the blood-vessels. And yet the whole *raison d'être* of the circulatory system is the existence of the tissues. Normal lymph-formation and œdema-formation must be the ultimate result of at least two processes, one in which the tissue cells are paramount, the other in which the blood-vessels themselves are paramount.

It is a physiological law that anæmia of a tissue is followed by active congestion, and though the vascular condition is apparently identical with that produced by section of the vaso-motor nerves, the results in the two cases are widely different. For in active congestion the lymph-flow is increased, in paralytic congestion it is not increased.[1] Now the essential difference between the two kinds of congestion, so far as the tissues are concerned, is that before active congestion occurs, the tissues have been deprived of food, whereas, before paralytic congestion occurs, they have not been deprived of food. We shall see later that the starved condition of the tissues and the increased output of lymph must be directly connected with one another as cause and effect. Whether the connection is a purely physical or is a vital one, it is as yet impossible to say.

But not only does starvation of the tissues lead to an increased output of lymph, the same result is produced when the waste products of metabolism are stored up in the tissues. Functional activity, like anæmia, is intimately associated with active congestion and its increased flow of lymph. In the case of a contracting muscle, it is known that exercise of function is accompanied by increased production of waste products, and part of the increased lymph-flow must be directed towards their removal. For it has been shown experimentally, in the case of a contracting muscle outside the body, that the chief cause of fatigue is not the deficiency of nutrition but the non-removal of the waste products which are formed by the muscle during functional activity.

We know, then, that when the tissues are starved, or when the products of functional activity are stored up in the tissues, an arterial congestion (active) occurs, which is accompanied by an increased flow of lymph. We also know that when an arterial congestion (paralytic) occurs in the absence of these tissue conditions it is not accompanied by an increased output of lymph.

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[1] At all events, for some hours. Since the changes in specific gravity described as occurring during œdema-formation, the subject under discussion, are recognisable during the first hour after the particular modification of the tissues which leads to œdema has been produced, the statement in the text is sufficiently near the truth for our purpose.

We must now consider the changes that take place in the tissues themselves after active and paralytic dilatation of arteries, respectively, have been produced.

The effect of paralytic congestion may be dismissed very shortly, for section of the sciatic nerve is not followed by any change in specific gravity of the muscle in the affected limb until several hours have elapsed after division of the nerve.

When active congestion follows anæmia there occurs a fall in the specific gravity of the tissues. Thus, if one hind limb of a dog be rendered completely bloodless by the application of an elastic bandage from the paw upwards, and this complete anæmia be sustained for three hours, it will be found, a short time after removal of the bandage, that the specific gravity of muscle of the affected limb is lower than the specific gravity of corresponding muscle in the unaffected limb.[1] When active congestion follows storage *in situ* of the metabolic products of functional activity, there also occurs a fall in specific gravity of the tissues. This can be shown in the following manner. Let the two gastrocnemii be removed from a frog with a length of nerve attached and be placed in a vessel of oil, and let one of the muscles be caused to contract until, with a maximal induced current, a minimal contraction occurs. If now the two gastrocnemii be removed from the oil simultaneously, and be placed in normal saline solution for a few minutes, it will be found on removing them that the muscle which has been caused to contract is of lower specific gravity than its fellow. This experiment can also be performed on the warm-blooded animal and without removal of the muscle from the body. Let the sciatic nerve of a dog be exposed, and after the limb has been rendered bloodless by means of an elastic bandage, let the nerve be stimulated with the interrupted current for a quarter of an hour and the products of functional activity be allowed to remain *in situ* for a further quarter of an hour. It will be found, a short time after removal of the elastic bandage, that the specific gravity of the muscle in the affected limb has fallen. It is important to note that the fall in specific gravity observed in this experiment is greater than can be explained by the anæmia alone. Though the anæmia here only lasts half an hour, the fall in specific gravity of the muscle is greater than when anæmia, in the absence of functional activity, has lasted for three hours.

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[1] During the period of anæmia, owing to the removal of blood and lymph by the pressure of the bandage, the specific gravity of muscle in the anæmic limb is higher than that of corresponding muscle in the unaffected limb.

The chain of evidence is therefore complete. A tissue is starved or there are stored up in it the products of its own metabolism. In some way this condition of the tissue is followed by arterial congestion and increased output of lymph from the blood-vessels. One portion of this increase flows away by the lymphatics and is recognised by an increased flow from the lymphatics, another portion remains in the tissues and is recognised by a fall in the specific gravity of the tissues.

Now if a sufficient amount of this lymph remains in the tissues, the clinical condition of œdema is produced. It is easy to show that the increase in volume of the limb, which is one of the most conspicuous clinical signs of œdema, occurs under perfectly physiological conditions. Let the hand and fore-arm be rendered completely bloodless by means of an elastic bandage, and, after its volume in the bloodless condition has been taken with the plethysmograph, let the circulation again pass through the limb, and let the whole hand and fore-arm be placed in a horizontal position in a bath of water at 40° C. for half an hour. On removing it from the bath and again taking its volume in the bloodless condition with the plethysmograph, it will be found to displace a quantity of water not infrequently larger by 40–50 c.c. than it displaced before it had been subjected to the action of warm water. We know that warmth, locally applied, increases metabolism, we know that it induces arterial dilatation, and though in this case we do not actually know that the output of lymph is increased, we know that the volume of the limb is increased, and that the increase in volume is not due to the presence of an increased amount of blood in the limb alone. For the volume of the limb was taken before and after the experiment in the bloodless condition. We know further that the increased volume of the limb is absolutely dependent upon the continuance of the circulation through the limb while it is in the bath, for if it be kept bloodless during the whole experiment, no change in volume takes place. We are bound to conclude that this increase in volume of the limb depends upon the fact that the tissues contain more fluid than before, while the method of rendering the limb bloodless, which at the same time expresses the lymph which is in the lymph spaces, favours the probability that the excess of fluid is contained rather in the tissue cells themselves than in the spaces between the tissue cells.

Under normal physiological conditions, therefore, when the tissues require nutrition, and when they are producing a greater amount of metabolic products, they increase in volume by holding a greater amount of fluid, and that in spite of the fact that no *primary* modification of the blood-vessels has been produced. In other words, when the tissues require more lymph, the blood-vessels supply it through the medium of arterial dilatation, but when the tissues do not require more lymph, though arterial dilatation and increased capillary pressure may be present, the blood-vessels do not supply it. It is the tissues themselves that determine whether they shall hold more lymph, and whether more lymph shall be poured out by the blood-vessels or no, and not the blood-vessels.

Now under all circumstances in which œdema occurs there is present starvation of tissues or storage in the tissues of the metabolic products of their own activity, or both of these conditions together.

(2) *In Œdema after Ligature of Arteries.*—In œdema which occurs after ligature of an artery, starvation of the tissues is manifest. Surgery provides a perfect example of this variety in the œdema of the leg and foot which is not infrequently seen after the femoral artery has for any reason been ligatured in Hunter's canal. Increase of venous pressure is here out of the question. A circulation is going on through the limb, otherwise

œdema could not show itself, but gangrene would show itself instead; and since the endothelium of the blood-vessels is in closer relation with such blood as passes through the blood-vessels than the tissue cells, the endothelial cells must suffer less than the tissue cells from lack of nutrition. The great starvation of the tissues of the limb in this case cannot be fully relieved until the blood-supply again returns to normal by the full establishment of collateral circulation, hence until that collateral circulation has been fully established, the tissues are perpetually calling for more nutriment, the blood-vessels are endeavouring to supply that demand but cannot meet it. They pour out lymph to their utmost and a part remains in the tissues to constitute the œdema fluid. As the collateral circulation becomes established and the blood-supply of the limb becomes greater, the amount of nutriment that can be supplied to the tissues by the blood-vessels is increased, the starvation of the tissues is satisfied, their demand for lymph ceases, an excessive amount of lymph is no longer poured out by the blood-vessels, such excess of lymph as was held by the tissues during their period of starvation drains away by the lymphatics, the œdema disappears. The œdema sets in when starvation of the tissues sets in; it disappears when starvation of the tissues disappears.

(3) *In Cachectic Œdema.* — Starvation of the tissues also plays a very prominent part in cases of cachectic dropsy. To take three typical examples. Œdema of the ankles often occurs at the latter end of the three conditions, pulmonary tuberculosis, malignant disease, malaria. In each of these diseases the tissues in the neighbourhood of the ankles receives a deficient supply of nutriment. In pulmonary tuberculosis the heart is small and ill-nourished; in malignant disease a large quantity of blood is diverted from the body generally for the supply of a tissue which is physiologically outside the body; in malaria there is a great destruction of red blood-corpuscles, and the constitution of the blood as a whole is altered. It is unnecessary to pursue these examples further.

(4) *In Chlorotic Œdema.*—Chlorotic œdema is associated with

an altered condition of the blood both as concerns the red blood-corpuscles and as concerns the blood-plasma. That the nutrition of the tissues in chlorosis is modified is amply shown by the inefficient way in which they discharge their functions. As has already been said, in some cases of chlorosis a renal element is probably present. It is also possible that the condition may in part be due to the action of toxic substances absorbed from the intestine, as was suggested by Sir Andrew Clark.

(5) *In Inflammatory Œdema.* — That inflammatory œdema is associated with need of the tissues for increased nutrition is shown by two facts. In the first place, referring to the experiment in which the hand and arm are placed in water at 40° C., it is only necessary to increase the temperature of the water, say, to 45° C. and inflammation is produced. The same changes occur in the limb as occur when the temperature of the water is 40° C. when inflammation is not produced. There is arterial dilatation in both cases, the temperature of the limb is increased in both cases, the volume of the limb is increased in both cases, the tissues contain a greater amount of lymph in both cases. The only difference that obtains is that the changes are more marked in the case in which the bath was at the higher temperature. It is this variety of œdema that was regarded by Cohnheim as essentially dependent upon an alteration of the vessel wall. But if alteration there be, it is produced, though to a lesser extent, under physiological conditions, and since we were obliged to connect the physiological increased output of lymph and the physiological increase in volume of the tissues with increased demand of the tissues for nutrition, we are also obliged to conclude, in the case of inflammatory œdema, that it too depends upon the increased demand of the tissues for nutrition. We cannot draw a line between the two processes and say, *this* is physiological and depends upon one set of causes, *that* is pathological and depends upon another set of causes.

In the second place, inflammatory œdema can be produced when the nutrition of the tissues is lowered by the action of an irritant which does not primarily involve the blood-vessels. Thus, if under perfectly aseptic conditions a small lesion be made in the centre of the cornea with a knife, the action of the irritant is momentary, and the inflammatory vascular changes accompanied by exudation of lymph which subsequently occur are not due to the direct action of the irritant, but are due to the nutritive changes in the avascular corneal tissue which that irritant has produced. The needs of the tissues, therefore, play an important part in the causation of inflammatory œdema.

(6) *In the Œdema of Passive Congestion.*—In the œdema which accompanies venous congestion, starvation is no less present than it is in other varieties of œdema, though it is less obvious. It is clear, however, that the diminished velocity of the blood-flow which is occasioned by obstruction to the venous output, is productive of an insufficient nutrition of the part. But in this form of œdema we have also to deal with the non-removal of waste products from the tissues. The effect of storage of these waste products upon the output of lymph has already been described, and it has been said that this factor is more potent than simple anæmia. This is what might have been expected, for starvation alone is a less serious condition than starvation combined with poisoning of the tissues. In accordance with this expectation it is found that some of the most marked clinical examples of œdema are those in which the two factors co-exist.

It might be urged that in starvation produced by simple anæmia, the tissues also form katabolic products, and no doubt this is true, but whereas in complete anæmia (to take an example) the tissues form katabolic products as the result of their vitality alone, in venous congestion they commonly form katabolic products as the result not only of their vitality but also of their functional activity. When the femoral artery is ligatured in Hunter's canal, functional activity of the lower limb is abolished by the very nature of the case, but when the venous pressure is increased in a case of heart disease, the patient commonly walks about for some time after the amount of œdema has been as great as ever it is in a case of ligature of the femoral artery. Moreover, in the case of ligature of the artery, no interference is placed in the way of the removal of waste products by the lymphatics, but in the case of cardiac disease, even if we leave all consideration of the effects of gravity on one side, an obstacle is still placed in the way of lymphatic flow by the increase of venous pressure which obtains at the orifice of the thoracic duct. No doubt even in the examples given, these are not all the factors in determining the different amounts of œdema, but the experiment which shows that half an hour's simple anæmia, combined with storage *in situ* of the waste products of tissue-metabolism, leads to a greater fall in specific gravity of muscle than three hours' anæmia without the storage *in situ* of such waste products, seems conclusive evidence of the important part played by katabolic products in determining the amount of œdema.

An apparent difficulty arises in this connection in the fact that starvation of a tissue and storage *in situ* of tissue waste products are normally accompanied by active congestion, during which the arteries are dilated and the limb becomes flushed and warmer to the touch, whereas in passive congestion the limb is bluish in colour and not red, and is cooler to the touch, not hotter. But the difficulty is apparent and not real, for though active dilatation of blood-vessels normally means a more rapid flow of blood through the limb, this is not a necessary concomitant of the condition. If the sciatic nerve be divided, the arteries are dilated, the limb is reddened, the temperature is increased, and the circulation through the limb is more rapid than normal; but if the flow of blood through the veins be obstructed, the velocity of the blood-flow through the capillaries is diminished, the oxyhæmoglobin of the blood becomes reduced to a greater extent than normal, and the limb takes on a bluish hue, while at the same time a greater amount of heat is lost from each volume of blood in the limb by radiation and evaporation, and the limb becomes cooler than normal. And yet the paralytic arterial dilatation is in existence just the same. So also in the œdema of passive congestion, though we cannot recognise active dilatation of the arteries by redness and increased warmth of the limb because of the venous obstruction that is present, we may confidently assume that such an active dilatation really exists. For we know by experiment that it sets in after a perfectly normal manner when severe anæmia or storage of waste products in the limb has been produced, and that when it is in full existence increasing the venous pressure in the limb, though it intensifies other processes, also causes the raised temperature of the limb to be replaced by a lower temperature, the reddish hue by a bluish hue.

(7) *In Œdema accompanying Renal Disease.*—Renal dropsy is of three kinds, corresponding to the acute tubal, the chronic interstitial, and the lardaceous varieties of renal disease. The œdema which accompanies each of these varieties is not of one and the same kind, though the fundamental principles underlying the different forms of renal œdema are identical with those which we have already considered. In dropsy accompanying acute nephritis starvation of the tissues is far less marked than their poisoning by the waste products of tissue-metabolism. For the condition of the kidney is such that there is serious interference with the removal of waste products by that organ. The inverse ratio which holds between the amounts of dropsy and of urine secretion in cases of acute nephritis, is well in accordance with this view. Besides the storage of waste products in the tissues there probably also assists in the production of renal dropsy the process which we shall see, when discussing transfusion, occurs when the volume of the blood is increased. Since the renal condition is such that the excretion of water is impeded, it is highly probable that in acute renal disease there is a certain amount of hydræmic plethora; if this be so, the share which the tissues normally take in preserving the volume of the blood at a constant level, must tend towards an increase of the dropsy.

The dropsy of acute nephritis is commonly greater than that which accompanies any other condition, and it makes its appearance in a remarkably short time. Not infrequently œdema is recognisable within twenty-four hours of the onset of the nephritis. The explanation of these facts, in my opinion, is probably as follows. The renal condition is such that the removal of the waste products of tissue-metabolism by that organ is in whole or in part abolished.

Waste products, therefore, accumulate in the blood, and when a tissue, by making a demand upon the blood, leads to an active congestion and to an increased output of lymph, that lymph presumably contains a greater proportion than normal of those very waste products of which the tissue is endeavouring to divest itself. In this way a vicious circle is established, and the œdema must continue to increase until the renal secretion is re-established. But this result follows not so much because the kidney fails to excrete water, and on that account leads to a hydræmic plethora, as was supposed by Bartels, as because the kidney fails to excrete metabolic waste products and therefore leads to a storage of those waste products in the blood and tissues.

As in every attempt to explain renal dropsy so here, the fact that obstructive suppression of urine is only in the rarest cases accompanied by dropsy presents a difficulty. The great difference between anuria due to obstruction of both ureters, and anuria due to acute nephritis, lies in the fact, that under the former condition any modification of the blood which may be due to passage of the blood through the kidney is not necessarily prevented, whereas the converse must be largely the case in acute nephritis. It is not advisable here to forestall the remarks that will be made when we deal with these questions, but it may be pointed out that the symptoms accompanying the two forms of anuria are totally dissimilar. It is at least possible that the absence of dropsy in obstructive anuria may depend upon the fact that the waste products of tissue-metabolism (which are not normally excreted as such in the urine) undergo their normal conversion into urea. One thing is certain, urea and even urine may be injected in large quantities into the circulation of an animal whose renal arteries are ligatured without producing the symptoms of acute nephritis, and in particular without producing dropsy.

The dropsy which accompanies chronic interstitial nephritis, it has already been said, is very largely of a cardiac and not of a strictly renal type. But the subjects of chronic interstitial nephritis also become affected with an œdema which is strictly renal. This may depend upon the superposition of an acute upon the chronic change, and in those cases the œdema may be as marked as in a case of primary acute nephritis. But patients with chronic renal disease upon which no acute change has been superadded, and in whom there is no cardiac failure, nevertheless show an œdema. In these cases it is never considerable and, as a rule, is confined to the existence of a "puffiness" of the loose connective tissue about the eyes. The explanation of this œdema is not easy, for at the time at which it is present the excretion of urine is commonly increased considerably and not diminished. Nevertheless the excretion of urea is diminished, and there is reason to believe that in these cases the amount of nitrogenous waste product in the blood is increased; it is perhaps to this fact that the œdema must be ascribed. The subjects of chronic renal disease, moreover, are commonly pale and anæmic, and it is possible that chronic starvation of the tissues also plays a part in the process.

The dropsy which accompanies lardaceous disease of the kidney has always been a subject of much uncertainty on account of the marked differences which occur, especially in the cardio-vascular system, between this and other varieties of kidney disease which lead to œdema. Judging from the fact that the lardaceous material, as we shall see, is deposited in the coats of the blood-vessels, and that it causes a diminution in their calibre, it seems probable that the dropsy in lardaceous disease depends upon direct anæmia of the tissues, particularly as no compensation for the vascular change is made by hypertrophy of the left ventricle. To this it must be added that the chief causes of lardaceous change, namely, prolonged suppuration and syphilis, are eminently calculated to induce a cachectic condition, and, therefore, to bring the tissues into a devitalised or starved condition.

The lardaceous change is a general one and is not confined to the kidneys, though the kidneys are usually involved. We have therefore to distinguish between an œdema due to the lardaceous change proper (and this is almost certainly dependent upon simple starvation of the tissues), and an œdema due to lardaceous change in the kidney, which, it is probable, depends to a very large extent upon storage of waste products in the tissues; for the lardaceous kidney is very frequently, if not generally, the subject also of acute or sub-acute tubal nephritis. The majority of cases of lardaceous disease combine these two conditions to a greater or less extent. The œdema of lardaceous disease, even when the kidney is also the seat of acute renal changes, is commonly not great. The reason of this probably lies in the fact that most patients with lardaceous disease lose large quantities of water, owing to the severe diarrhœa and vomiting which arise from lardaceous changes in the blood-vessels of the gastro-intestinal mucous membrane.

(8) *In Œdema of the Lungs.*—Œdema of the lungs, apart from that variety which is associated with inflammatory conditions and which is seen in an extreme form in the coagulated exudation that fills the air-vesicles in acute pneumonia, is associated principally with cardiac disease and with acute renal disease. Cohnheim insisted that pulmonary œdema is stagnative, and depends upon failure to contract of the left ventricle while contraction of the right ventricle is still going on. Such a condition is brought about if the ascending aorta be ligatured in the rabbit. In the case of œdema of the lungs which is so frequently found after death, he believed that the failure of the left ventricle to contract is absolute, and that "a man does not die because he gets œdema of the lung, but he gets œdema of the lung because he is on the point of dying."[1] But where the pulmonary œdema supervenes some time before death, and where it supervenes but later disappears, it is obvious that the failure to contract can only be relative. Virchow taught that the œdema depends upon arterial congestion and venous stagnation, but Cohnheim pointed out that an arterial pressure so great as that produced by shutting out from the circulation three-quarters of the total sectional area of the pulmonary arteries, is not sufficient to produce œdema in the part of the lung supplied by the remaining vessels; and also that "every stenosis of the left auriculo-ventricular opening most plainly shows that the mere impeding of the venous efflux from the lungs is far from being sufficient in itself to give rise to transudation and œdema."[2]

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[1] P. 528, Engl. trans.

[2] P. 523, Engl. trans.

The subject is so fraught with difficulties from an experimental point of view that an explanation of pulmonary œdema is under any circumstances not easy. But in the case of cardiac disease, at all events, the fact that œdema of the lungs is as much a sign of failure of the right ventricle as is œdema of the ankles, and the fact that in renal disease, whether acute or chronic, the presence of a small amount of œdema at the base of the right lung often is one of the earliest signs of a large accession of dropsy throughout the body generally, render it probable that pulmonary œdema is essentially dependent upon the same processes as œdema elsewhere. It is tacitly assumed, both in Virchow's and in Cohnheim's explanation, that the œdema fluid in pulmonary œdema is poured out by the pulmonary blood-vessels. But the existence of a true inflammatory œdema of the lungs renders it possible if not probable that these blood-vessels are not the source of the exudation at all. Inflammatory œdema in the body generally is accompanied by arterial dilatation and the presence of arterial blood, but in the lungs the arterial blood is included in veins whose walls are in the highest degree unlike those of the systemic arteries. So that short of actual demonstration one is inclined to doubt whether inflammatory œdema fluid is put out by the pulmonary blood-vessels, especially when one remembers that the lung tissue proper is supplied by the bronchial arteries which are of systemic origin. It is far more probable that pulmonary œdema of all kinds is produced by an excessive output of lymph from the bronchial blood-vessels. If that be so, the explanations that have been already given of cardiac and renal dropsy may readily be applied to the lungs also. Nevertheless this solution of the question must not be regarded as more than a possible one, though there can be no doubt that in cardiac failure the nutrition of those parts which are supplied with blood by the bronchial arteries must suffer, and that in acute nephritis those same parts must be poisoned by the accumulated waste products of metabolism that are circulating in the blood.

($\gamma$) *Importance of Blood-Vessels in Œdema-formation.*—But though the author insists upon the importance of the tissues in determining the occurrence of œdema, he must not be supposed to deny any part to the blood-vessels. On the contrary, it has already been pointed out that in lymph- and in œdema-formation there must be one phase of each process in which the blood-vessels are paramount. Whether the changes initiated by the blood-vessels are physical or vital is an open question, which after the recent discussion we may leave on one side, but there is no doubt that the blood-vessel walls are altered in œdema-formation.

It has been said that active congestion follows anæmia. In accordance with this law, severe anæmia of the hind limb of a dog, produced by application of an elastic bandage and maintained for three hours, is followed by active congestion, as shown by redness of the limb, increase of temperature, and an output of lymph so great as to lead to an œdematous condition of the tissues. But the blood-vessels are not only altered in the respect that there is a greater output of lymph than normal, they are altered in that they react to an increase of venous pressure in a manner absolutely different from that in which they react when active congestion is absent. Attention has already been drawn to the fact that in the absence of active congestion increase of venous pressure for one hour does not lead to an increased output of lymph, but when active congestion is present and œdema is making its appearance, the output of lymph increases as the venous pressure is raised, returns to normal as the venous pressure is allowed to return to normal. In other words, when œdema is coming on, the blood-vessel walls react to increase of venous pressure like simple physical membranes. Whether this is the case with the degree of active congestion which occurs in normal physiological life is at present unknown, but that it is true of the great active congestion which accompanies œdema-formation after severe anæmia or the storage of metabolic waste products in the tissues, is certain.

Apart from these changes the blood-vessels must be altered in another way. In the vast majority of cases, the factors that determine starvation and storage of waste products in the tissues, must also determine starvation and storage of waste products in the cells composing the blood-vessel walls themselves. In the case of inflammatory œdema, for example, it is only in special cases that the irritant fails to act on the blood-vessels of the part at the same moment that it acts upon the tissue cells. And just as it is unreasonable to suppose that starved and poisoned tissue cells can discharge their function normally, so it is impossible to imagine that a membrane of starved and poisoned endothelial cells can discharge its function normally whether we regard it as a filter or as a secreting organ. The function of that membrane must be altered, and with it the composition of the fluid that has passed through the membrane must be altered also. From the very nature of the case it is essential that œdema fluid should differ from normal lymph, and that specimens of œdema fluid should vary according to the degree in which the function of the blood-vessel wall is modified.

But it is difficult if not impossible to separate the action of a substance upon the blood-vessel walls from its action upon the tissue cells, and though Heidenhain has shown that such substances as leech extract, mussel extract, etc., produce an increase of lymph-flow, and Hamburger has described a micro-organism whose toxic products lead to œdema, it cannot be regarded as certain that these substances act upon the endothelium of the blood-vessel walls directly as the authors mentioned would have us believe, rather than indirectly through the medium of the tissue cells.

I have examined microscopically the capillaries and small veins of the frog in many cases in which there was œdema, but have found no change, either histological or histo-chemical, excepting actual rupture of the vessels due essentially to the manipulative interference. Even when the œdema is extreme, as, for example, in the case of frogs that have been curarised and allowed to remain in a damp atmosphere, no vascular change could be recognised either by attempts at staining during the life or after the death of the animal. Arnold, in inflammatory œdema, has described the cement substance between the endothelial cells composing the capillary wall as being altered. In normal specimens stained with nitrate of silver the cement substance is represented by a number of very narrow lines of a fairly constant thickness, but when the vessel is inflamed Arnold describes these lines as presenting a beaded appearance, and the so-called "stomata" as being more evident. Excepting the alteration in quantity and quality of the lymph which accompanies inflammation this is the only evidence which we possess that the constitution of the blood-vessel walls is changed when œdema occurs. But the meaning of this capillary change, even if it be a real and not an artificial one, is of course quite uncertain. Engelmann goes so far as to assert the possibility that the so-called "stomata" in blood-vessels are themselves artificial productions.

(δ) *Explanation of the Distribution of Œdema.*—It has already been said that the distributions of cardiac and of renal dropsy are different, cardiac œdema showing itself first and principally in those situations where the action of gravity is greatest, as at the ankles, renal œdema in situations such as the face, where the action of gravity is apparently set aside. The explanation of these differences in distribution must now be examined a little more closely.

(1) *Cardiac Œdema.*—The characteristic distribution of cardiac dropsy is usually regarded as strong evidence of the mechanical causation of passive œdema, for it is obvious that when venous pressure is increased generally by the condition of the heart, the effects of that pressure must be increased by gravity to a greater extent in the capillaries of the foot than elsewhere in the body. Of the bare fact that cardiac œdema shows itself first in the neighbourhood of the ankles there is of course no doubt, and it will immediately be seen that this distribution of the dropsy is rightly held as being dependent upon gravity. But since we have rejected the view that the œdema of venous congestion depends upon increase of venous pressure *per se*, it is necessary to show how it is possible to explain the characteristic distribution of the dropsy, on the assumption that the œdema is primarily caused by an endeavour of the blood-vessels to supply the needs of the tissues and to provide a means for the washing away of the products of tissue-metabolism.

Œdema does not show itself in cases of cardiac disease until general cardiac failure sets in. So long as compensation is fully maintained, œdema and the other symptoms of heart failure remain in abeyance. With the onset of general cardiac failure the pressure in the systemic veins is indeed increased, but the force and efficiency of the left ventricle are diminished also. Therefore in general cardiac failure all parts of the body must suffer—not necessarily to an equal degree but necessarily to some degree—from starvation of the tissues due to changes on the arterial side. In addition, the increase of venous pressure retards the flow of blood through the tissues, and hence the changes on the venous side add to the starvation of the tissues, while at the same time they impede the removal of waste products from them. Under these circumstances one would expect that the œdema should show itself all over the body, in the hand, for example, as well as in the foot. But it must be remembered that experiment has shown that when œdema is coming on, the output of lymph from the blood-vessels varies directly with the venous pressure (*i.e.*, with the capillary pressure). Now the capillary pressure is normally greater in the foot than in the hand, principally owing to the fact that the lower limbs, and especially the legs and feet, are commonly in the dependent position, while the fore-arms and the hands are more commonly horizontal or even somewhat elevated. So that even if starvation of the tissues and the storage of waste products in the hand were as great as they are in the foot, which again, owing to gravity, they are not, it would be essential that the œdema should show itself first in the foot. When, therefore, the conditions are such that œdema is coming on, gravity determines that the greatest output of lymph shall take place in the foot, and since gravity also offers a greater opposition to the removal of the lymph from the foot than from the hand by way of the lymphatics, a collection of fluid sufficiently great to be recognised macroscopically takes place in the foot at a time when it is absent or cannot be recognised in the hand. Though mechanical factors do not *per se* determine the changes which lead to the onset of œdema in cardiac disease, they take a large share in determining the distribution of the œdema when those changes have been brought about, as well as in determining the time at which those changes shall occur in different regions.

(2) *Renal Œdema.*—In the dropsy of acute renal disease the metabolic products of the tissues are circulating in the blood, and for this reason all parts of the body must suffer. In this respect there is similarity between renal and cardiac causes of dropsy, but here the similarity stops, for in uncomplicated renal disease, cardiac failure and all its consequences are absent, and the left ventricle readily overcomes the effects of gravity. For this reason the œdema does not first show itself in the lower extremities but in those parts of the body where the tissue is loosest, where the output of lymph is least impeded, and where the presence of an increased output of fluid is most easily recognised. Of all situations the eyelids fulfil these conditions best, but if care be taken it will be found that a small amount of œdema may be recognised simultaneously in other regions also where the subcutaneous tissue is loose. Sufficient has already been said concerning the dropsy which occurs in chronic renal disease complicated by cardiac failure and in lardaceous disease to render any special remarks upon the distribution of the dropsy in these conditions unnecessary.

But questions as to the distribution of dropsical fluid cannot be dismissed quite so summarily.

When œdema affects one and the same tissue, it is readily intelligible that the œdema should be most evident in parts where that tissue is loosest, for mechanical factors play their part in œdema-formation and distribution. It is obvious that the output of fluid depends upon the resistance to that output offered by the density of the tissues, so that there is no difficulty in understanding that, when œdema shows itself in subcutaneous connective tissue, it appears sooner and is more marked about the ankles than over the tibiæ, or in the eyelids than over the pinnæ of the ears. But, on the other hand, though it might be expected, for example, that the dropsy of acute renal disease should affect all tissues of the body alike, the autopsy of a person who has succumbed to acute nephritis reveals the fact that the excess of lymph shows itself more in some situations than in others. Thus there may be great effusion into the pleural and peritoneal cavities, while the pericardial cavity contains little if any more fluid than normal; there may be extreme œdema of the subcutaneous connective tissue over the whole body and but little excess of fluid in the serous cavities, and so on. Again, when the lower extremities become œdematous as the result of cardiac disease, the excess of fluid is contained in the skin and subcutaneous tissue rather than in the subjacent muscles. So also in extreme hydræmic plethora, Cohnheim and Lichtheim found that the fibrous tissue of the salivary glands and pancreas become œdematous, and not the gland substance itself. And in renal disease and in venous obstruction it is the subcutaneous connective tissue and adipose connective tissue and the serous cavities which become dropsical, while such tissues as the skeletal muscles, the heart, and the brain remain free.[1] Indeed it may be stated generally that when œdema shows itself in a complex mass of tissue, it is most manifest in those parts of the mass which, physiologically, are of the least importance to the economy.

Now at first sight it is difficult to reconcile these facts with the view of œdema which has been put forward in the preceding pages. At first sight it might be supposed that tissues such as the brain and heart, which are extremely sensitive to alterations in the quantity and quality of their blood-supply, would suffer first and to the greatest extent from deficient nutrition or storage *in situ* of metabolic waste products; that, in other words, if the author's explanation of œdema is correct, the brain and heart should be the first organs to show œdema, and should show it to the greatest extent. The brain can ill bear starvation, and since its demand for nutrition is greater than that of the skin when both are starved or poisoned by the same cause, one might expect that the brain should become œdematous while the skin is normal, whereas actually the converse is the case.

An explanation of this apparent paradox is suggested by

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[1] It is open to doubt whether in extreme cases the "nobler" tissues are not in some degree œdematous; in the case of muscle, at all events, it has been shown experimentally that the onset of œdema is accompanied by a fall in specific gravity; the brain, too, of persons dying with renal dropsy is often "watery."

Voit's researches on the proportionate losses in weight which the various organs undergo in starvation. Voit found, on depriving animals of food over a prolonged period, that those tissues which are of the greatest importance to the economy are nourished at the expense of those tissues which are of less importance. Thus the brain and spinal cord lose only 3 per cent. of their weight in a hunger period during which fat loses 96 per cent. Now, in the starvation which leads to œdema it is likely that the same law holds good, and since the brain, for example, gets its full complement of food when the heart is failing or when there is renal disease, it follows that not only must the less important tissues, such as fat, skin, etc., get a diminished supply dependent upon the cardiac or renal cause, but that that diminution must be further augmented by reason of the deficiencies which are being made up in the brain. The brain, therefore, does not suffer,[1] but the skin, etc., suffer doubly. It is no cause for wonder, therefore, that œdema manifests itself principally in the skin and serous cavities.

(ε) *Source of Œdema Fluid.*—The fluid which enters a part and constitutes œdema comes, of course, immediately from the blood, but in the case of localised venous congestion and localised anæmia, at all events, this is not the end of the matter. For it has already been said that whereas there is a fall in the specific gravity of the muscle and skin of the limb in which œdema occurs, there is a rise in the specific gravity of the muscle and skin elsewhere. The tissues, therefore, of the body at large give up water, or rather lymph, to the blood to supply that loss of lymph from the blood which is taking place in the region of œdema. It is probable that the process whereby this output of lymph from muscle and skin into the blood takes place, is the converse of that which leads to an intake of lymph by muscle when a condition of apocoptic plethora has been produced (chap. xi.). But there are also reasons for believing that a part of the body which needs an increased supply of lymph (the part which is becoming œdematous) is able to make known its wants to the rest of the economy, whereby other parts are able to assist in meeting that demand and to prevent the whole stress from being felt by the blood. We shall see later that in collapse the specific gravity of the blood is for some time maintained at a constant level in this way. This fact is an additional proof—if one be needed—of the importance of the tissues in the pathology of œdema.

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[1] See note, previous page.

If we attempt to define œdema-formation, therefore, we may say that it is *an excess of the normal process whereby the nutrition of the tissues and the removal of their waste products are carried out.* We must conclude that œdema-formation, like lymph-formation, is the ultimate result of two sets of phenomena, one in which the tissues are paramount, the other in which the blood-vessels are paramount. Of these two sets of phenomena, the first, in my opinion, is the most important, but the second is the one upon which stress is laid by most authors at present. As to whether lymph-formation and œdema-formation are entirely explained by our present knowledge of physics and chemistry, or are in great part dependent upon processes which, for lack of a better name, we may call vital secretory, is uncertain, but in my opinion the bulk of evidence is in favour of the latter interpretation ; in this respect I agree with Heidenhain and Hamburger.

We have dealt with the accumulation of lymph in the tissues and in the serous cavities, and have shown how such accumulation depends upon a disturbance of the normal equilibrium which exists between blood, blood-vessels, tissues, and lymphatics. This equilibrium is unstable, and that a tissue does not become œdematous — in the pathological sense of the term — under normal circumstances depends upon the fact that an equilibrium can still be maintained in spite of marked alterations in the conditions of the component forces. It is true that a healthy tissue, which is the seat of increased metabolism (for example, the hand and arm when immersed in warm water) under normal conditions, *tends* to become œdematous in that it contains a greater amount of lymph than when its metabolism is not increased. That it does not become pathologically œdematous simply depends upon the fact that the reserve power of the heart and the degree of dilatation which the arteries can undergo are such, that an amount of blood and of lymph can be supplied to the part far greater than is necessary to supply the increased demand of the tissues. The tissues demand more lymph than normal, but their demands can be supplied at once and in full by the vascular system; starvation and storage of waste products are kept within manageable limits. But when there is some failure of the central organ, as in cardiac disease, or when there is an impediment to the circulation, as in the case of a tight ring or bandage, the action of which is prolonged, or when there is an insufficient supply of blood to meet the normal requirements of the tissues, as after ligature of the main artery of a limb, starvation or storage of waste products, or both together, occur to so great an extent that the maximum endeavours on the part of the circulatory system are insufficient to meet the demands of the tissue. However much lymph may be poured out there still remains a stimulus for the output of more, and since the capacity of the lymphatic system is limited this lymph cannot be carried away as rapidly as it is formed: a portion of it remains in the tissues and œdema results.

From this it follows that if the demand of the tissues can be sufficiently lessened to be brought within the limits of the supply, whether that supply be normal or abnormal, the demand of the tissues and the output of lymph will cease, so that in time the excess of lymph will drain away from the tissues and the œdema will disappear. That this sequence of events happens is shown very clearly by the effect of rest on a patient with commencing heart failure and œdema of the legs. When the patient is walking about, the demands of the tissues are the sum of the demands made for the maintenance of life of the tissues, and the demands made for the exercise of functional activity by the muscles. For these demands the vascular system is not sufficient, and hence the œdema. But when the patient is at rest in bed the demands made for functional activity to a large extent cease, and the vascular system, though unable to meet the double demand, is equal to meeting the diminished demand; the œdema rapidly disappears. At a later stage of the cardiac failure, however, the supply is not even equal to the one demand made by the tissues for the maintenance of their life, and œdema reappears. Under these circumstances, though it is no longer possible to reduce the demand of the tissues, equilibrium may be re-established by increasing the supply. This can be done by the aid of cardiac tonics such as digitalis, strophanthus, strychnine, iron, etc.; these drugs improve the nutrition of the myocardium, lead to a more satisfactory ventricular contraction, and again œdema disappears. But in the case of every cardiac patient, if the condition run a natural and uninterrupted course, there comes a time when at last the heart can no longer be braced up, and when, aided to the utmost by drugs and by reduction to a minimum of the demand, it is nevertheless unable to meet the requirements of the tissues. Dropsy now never leaves the patient, but, from causes that can readily be understood, the condition goes from bad to worse until death closes the scene.

(ζ) *Absorption of Œdema Fluid.*—There is no doubt that the removal of exuded fluid is carried out by the lymphatics, and when the tissues are the seat of the exudation and the amount of exudation is small, it is probable that the lymphatics alone are sufficient for the purpose. But when the amount of fluid is great, it is possible that the blood-vessels play a part in the process. Indeed in the case of collections of fluid in the serous cavities, whether introduced experimentally or during the course of disease, there is reason to believe that the blood-vessels may play a greater part than the lymphatics. Thus Starling and Tubby found, on injecting colouring matter (indigo-carmine and methylene-blue) into the pleural or the peritoneal cavity, that in eleven out of twelve experiments the colouring matter appeared earlier in the urine than in the lymph which flowed from the thoracic duct.[1]

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[1] Meltzer has recently (Nov. 20, 1897) published experiments showing the exact opposite. Perhaps a difference in the degree of anæsthesia employed by these authors accounts for the differences in their results. I certainly cannot entertain the suggestion put forward by Meltzer that Starling and Tubby's results were due to leakage into the urine of coloured fluid from the abdominal cavity.

All varieties of fluid are not absorbed at the same rate, whether from serous cavities or from connective tissue spaces. It has been found experimentally that watery solutions of crystalloids are absorbed with much greater rapidity than fluids containing proteid. Amongst watery solutions of crystalloids, too, the rapidity of absorption is greater as the solution is more dilute. The same differences are observed clinically; in fact, pathological exudations into the serous cavities, if they contain a considerable amount of proteid, are often absorbed with extreme slowness or not at all. Whether a solution introduced into a serous cavity, or into the connective tissues experimentally or for therapeutic purposes, be a purely watery one or no, after a shorter or longer time such fluid as remains at the seat of injection is found to contain albumen. In the case of a solution of a crystalloid, if the degree of concentration be above a certain point, the volume of fluid injected into the serous cavity or connective tissue increases at first, owing to the output of fluid from the blood-vessels.

The process whereby absorption of fluid takes place, in so far as it takes place by way of the blood-vessels, forms a part of the whole controversy as to the physical or vital function of the blood-vessel walls. We have already dealt with this controversy in the case of lymph-formation and œdema-formation at some length, and it is unnecessary to enter so fully into the subject of absorption.

(1) *Part played by the Lymphatics.*—It may be taken as certain that one portion of absorption is carried out by the lymphatics. The lymph is urged along the lymphatics mainly by the aid of muscular contraction of the parts in which the lymphatics lie, aided perhaps by the contractility which, according to Camus and Gley, resides in the walls of the thoracic duct. Concerning this portion of the process nothing more need be said.

(2) *Part played by the Blood-vessels.*—In investigating the part played by the blood-vessels in absorption, Heidenhain introduced salt solutions of known strengths, which were different in different experiments, into a loop of intestine shut off from the rest of the gut by ligatures. After a certain time the

loop was opened and the fluid contents collected and analysed. Heidenhain found that saline solutions whose freezing points were equal to or higher than that of the blood-serum of the animal under experiment were absorbed, and this he regarded as being due chiefly to osmosis. But since he found that solutions whose freezing point was lower than that of the serum were absorbed also, and that, after exposing the intestinal mucous membrane to the action of sodium fluoride (which destroys the vitality of the epithelium), the absorption which occurs is different from that which occurs when sodium fluoride has not been used, and is explicable on physical principles alone, he concluded that besides the physical part of absorption there is a part which is dependent upon the life of the epithelium.

Starling for a time was inclined to allow that absorption from the pleural cavity cannot be explained on physical principles alone, but in his later work he abandoned this view, and holds that absorption, so far as the blood-vessels are concerned in the process, essentially depends upon osmosis and dialysis. Of course he only regards these processes as being concerned with the absorption of water and crystalloids; the proteid constituents of exudations, he considers, are absorbed by way of the lymphatics. In the osmotic process he ascribes the chief part to the possession by proteid substances of a small but definite osmotic pressure. The experiments, however, by means of which he seeks to establish this point are not, to my mind, convincing. With regard to the absorption of highly albuminous fluids from the serous cavities and connective tissue spaces, Starling maintains that there is no sufficient evidence that such fluids are absorbed by the blood-vessels at all, and that the very slowness with which they are absorbed is probably an indication that absorption is carried out " mainly, if not exclusively," by the lymphatics.

Hamburger found that absorption from the peritoneal cavity takes place even twenty-four hours after the animal has been killed, and that no difference is made whether the endothelial cells of the peritoneum have or have not been killed by the action of heat or of any chemical substance. He therefore rejects the vitalistic explanation, and since, as Heidenhain had pointed out, fluids with a lower freezing point and therefore a higher final osmotic pressure than serum are absorbed, as well as those with an equal or a higher freezing point, he also rejects osmosis as the effective agent. He ascribes absorption to the physical process of imbibition. According to Fick two kinds of imbibition may be recognised: (1) molecular, *i.e.*, the sucking up of fluids by homogeneous substances, such as gelatine, agar-agar, etc.; (2) capillary, *i.e.*, imbibition into porous materials, such as porcelain, connective tissue, etc. Hamburger suggests that when fluids are present in the peritoneal cavity, the cement substance between the endothelial cells, and possibly the cells themselves, take up the fluid by molecular imbibition. Then by capillary imbibition the fluid is taken up into the connective tissue spaces, where a small part is removed by the lymph-stream. The remainder is sucked up by the cement substance between the endothelial cells of the blood-vessel walls or even by the cells themselves. The power of imbibition by a tissue being limited, in a short time the maximum swelling would be reached and absorption would cease were it not that the blood-stream continually removes fluid taken up by the capillary walls. He found that he was able artificially to simulate the process and produce absorption of serum.

Now previous to any discussion of the mode whereby absorption takes place, it is necessary once more to point out that, so far as concerns the part that may be played by osmosis, considerations derived from determinations of freezing points are fallacious guides. It follows that there is grave doubt whether the so-called "hypertonic" solutions of all those authors who have introduced crystalloid solutions into the peritoneal cavity for experimental purposes are hypertonic at all, in the sense that, on physical principles, the flow of fluid should be from the blood-vessels into the peritoneal cavity. As a matter of fact, in the majority of cases, if not in all, the crystalloid solutions used were of such strengths that, on physical principles and *at pressures such as obtain in the animal body*, the flow of fluid should take place in the direction that it has done, viz., from the peritoneal cavity to the blood-vessels. The conclusions drawn by Heidenhain and by Hamburger lose force from the fact that the arguments are based upon false premises.

But even if the crystalloid solutions are of such a strength that no objection can lie on this score, the author's experiments seem to indicate that absorption of crystalloid solutions more concentrated than is necessary to produce osmotic equilibrium with the blood-plasma on the other side of the vessel wall, can take place ultimately by a combination of the physical processes of osmosis and dialysis. The reason of this depends upon the fact to which allusion has already been made, that the presence of proteid in a solution does not hinder dialysis to anything like the extent that it hinders osmosis.

If we place on one side of a membrane, in an artificial scheme, serum which is in osmotic equilibrium at atmospheric pressure with a 1·6 per cent. watery solution of sodium chloride, and on the other side of the membrane place a 2 per cent. watery solution of sodium chloride, at first fluid passes through the membrane by osmosis towards the salt solution. After a certain point of concentration has been reached on either side of the membrane the two fluids come into osmotic equilibrium and the flow of fluid ceases. But afterwards it recommences, but the *direction of the flow is reversed* and the serum increases in amount at the expense of the salt solution. The reason of this is as follows. While osmosis is going on from serum to salt solution, sodium chloride is dialysing through the membrane from the salt solution into the serum. On starting the experiment the amount of sodium chloride in the serum is approximately ·5 per cent., the amount of sodium chloride in the salt solution is 2 per cent.; hence dialysis will only cease when a 1·25 per cent. solution of sodium chloride is on either side of the membrane. Before this can be reached, however, the point of concentration (1·6 per cent.) of the sodium chloride solution necessary to produce osmotic equilibrium with the serum must be passed, and directly that point has been passed the osmotic flow of fluid changes its direction. It follows, therefore, that the experiments hitherto performed, which have shown the absorption of so-called "hypertonic" solutions, cannot be taken as evidence of the insufficiency of osmosis, as both Heidenhain and Hamburger would have us believe. If we apply this experiment to the animal body, and remember that such sodium chloride as may pass into the blood-vessels by dialysis is readily excreted by the kidneys, it is obvious that physical experiments indicate no limit to the degree of concentration which a crystalloid solution must possess, in order to put the possibility out of the question that absorption of crystalloid solutions takes place by a combination of the physical processes of osmosis and dialysis.

When the fluid in the peritoneal cavity contains proteid, the case is not greatly different, for it has been said that when two fluids, which differ from one another only in the amounts of proteid which they contain, are placed on either side of a membrane in an artificial scheme, the fluid which contains the greater amount of proteid increases in quantity at the expense of the fluid which contains the smaller amount of proteid. The reason of this appears to lie in the different degrees to which the membrane is clogged by proteid on the two sides. It is only when actual hæmorrhage has taken place that exact similarity in proteid content of the fluids is found inside and outside the blood-vessels; in all other cases the blood contains the greater amount of proteid, and hence on physical principles absorption up to a certain point can take place.

From the evidence afforded by physical experiment we may conclude that, when absorption takes place, it does so in the following way. Water passes from the effusion into the blood-vessels by osmosis and causes concentration of the salts in the effusion and dilution of the salts in the blood-plasma. Owing to the difference in concentration of the salts on the two sides of the membrane, dialysis is set up and salts pass into the blood-vessels from the effusion. These two processes must go on so long as the proteid composition of the effusion is lower than that of the blood, but as soon as the proteid composition of both fluids is identical, any absorption which may take place must probably be independent of osmosis and dialysis. If it depend upon physico-mechanical processes the remainder of the fluid probably is carried away by the lymphatics. A physical view of absorption such as has been sketched above agrees well with the fact that absorption of highly albuminous fluids, and in particular of blood-effusions, takes place with extreme slowness. In the case of blood-effusions it is certain that in part absorption takes place by the lymphatics. For when blood has been effused into the peritoneal cavity (after rupture of a tubal gestation, for example) the lymphatics of the anterior mediastinum and the lymph glands with which they are in connection are found engorged with blood. Absorption by the lymphatics, however, is slow, for they are few and small in comparison with the amount of fluid that has to be removed,[1] and since under such circumstances the parts that could be played by osmosis and dialysis are reduced to a minimum, it is intelligible that of all kinds of effusion, blood is absorbed with the greatest difficulty.

To conclude:—The possibility must be allowed that absorption of effused fluids is brought about in a physico-mechanical way. Upon this view, part of the fluid drains away by the lymphatics, part passes directly into the blood-vessels owing to osmosis and dialysis. Whether that explanation is considered a sufficient one, largely depends upon the view that is held concerning the secretory or physical nature of the blood-vessel wall.

NOTE.—The foregoing pages had already passed through the press before I was enabled, through the great kindness of Professor Schäfer, Professor Reid, and Dr Starling, to see advance sheets of the sections on "Diffusion, Osmosis, and Filtration" (Professor Reid), and on "The Production and Absorption of Lymph" (Dr Starling) in Professor Schäfer's—at that time unpublished—Text-book of Physiology for advanced students.

From our point of view, Reid's article is most important by reason of the stress which it lays upon the great complexity of the physical phenomena accompanying the interchange of water and of constituents of solutions through membranes, even when the membrane is dead. With regard to living membranes the two principal statements made by Reid are as follows:—"Whether permeability be a function of physical or chemical nature it is obvious that in the case of a living membrane the complex to which the term 'physiological condition' is applied must affect the property, so that one and the same membrane in the body may, under different circumstances, be more or less permeable by the same substance" (p. 276); and, in regard to the question whether in some cases the cells of a part take some active part in moving solutions across membranes, "so little is known of cell mechanics that if such a process does take place, we have certainly no conception of its *modus operandi*, and it is at least probable that a process considered to-day as a 'vital action,' may in the future become capable of a simpler explanation" (p. 283). This is no place to discuss the rival views of vital and physico-mechanical action, but I think it may be pointed out that the divergence between the two kinds of view is far less than it was fifty years ago. In the minds of most who use such terms as "vital," "vital secretory," &c., I think that the expressions have much the same meaning as the term "functional" in the expression "functional disease." At all events, in the preceding pages this is the meaning which I have attached to them. That in the broadest sense, life and its phenomena are built up of chemistry and physics, I suppose most modern "vitalists" would allow, and the real difference between them and their opponents consists in a difference of opinion as to whether our *present* knowledge of chemistry and of physics is sufficient to afford a full and satisfactory explanation of the phenomena under discussion. At the same time the supporters of "physical" views have shifted their ground and recognise that the crude physical views of fifty years ago had no conception of the complexity of the phenomena for which they were offering a solution.

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[1] The effects of coagulation of effused blood are purposely left out of consideration.

Starling's article on the production and absorption of lymph calls for less notice as his views have already been set forth in the preceding pages and have undergone no modifications since his later publications on the subject. In the case of absorption of serum, however, Starling extends somewhat his previous view that proteid is removed solely by the lymphatics, by attributing some importance to removal of proteid in the nutrition of the cells of the surrounding tissues.

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# CHAPTER VII.

## THE PATHOLOGY OF INFLAMMATION.

*Synopsis.*

- I. General Considerations. Description of Phenomena in Frog.
- II. The Dilatation of Blood-Vessels.
- III. The Exudation.
  - (i) Effects of Mechanical Conditions.
  - (ii) Characters of the Exudation: "False Membranes."
  - (iii) Meaning of the Exudation for the Economy.
- IV. The Cellular Elements of the Blood in a Region of Inflammation.
  - (i) The Red Corpuscles.
  - (ii) The Colourless Corpuscles. Chemiotaxis. Phagocytosis.
- V. Tissue Changes in a Region of Inflammation.
- VI. Causes of Variation in the Type of Inflammation.
  - (i) The Irritant:
    - (*a*) Effect of *Nature* of the Irritant.
    - (*b*) Effect of *Intensity* of the Irritant.
  - (ii) The Tissue on which the Irritant acts:
    - (*a*) Effect of Nature of the Tissue.
    - (*b*) Effect of Mechanical Conditions.
    - (*c*) Effect of Integrity or otherwise of Nervous Supply.

**I. General Considerations and Description of Phenomena in Frog.**—In spite of Thoma's remark that "Inflammation is a kind of protean idea which dates from the scholastic period of ancient medicine, and should be relegated to it as its undisputed property," it is necessary to consider the subject as if it were a definite entity instead of being a combination of phenomena. For so long as pathology is not divorced from medicine and surgery, it will be necessary to examine together the processes which combine to make up the most common of all pathological conditions. There is no doubt, as we shall see, that inflammation is protean, but in spite of diversity in shape the pathological principles underlying the conception of inflammation are everywhere the same, and the diversity of shape depends upon factors which may be highly important in determining the kind of inflammation that shall appear, but which, nevertheless, are unessential in considering inflammation broadly.

It is intelligible, from the frequency with which inflammatory conditions occur, that the subject of inflammation should have attracted the attention of the earliest writers. Hippocrates (B.C. 430) described the condition under the name of "φλεγμόνη," and at the present day some surgeons speak of "phlegmonous" erysipelas when they wish to imply that the course of the inflammation is peculiarly rapid and severe. Celsus (A.D. 32) drew attention to the most important characters of acute inflammation, and the redness, swelling, heat, and pain which he described have since his time been universally known as the "cardinal signs" of inflammation. To the four cardinal signs a fifth, "impairment of function," was added later, and, speaking generally, we find that these five signs are to be recognised in all cases of inflammation. At the very outset, however, it is necessary to state that the degrees to which the cardinal signs are present, differ in different cases; in one, swelling is inconspicuous, pain is severe, in another, redness is inconspicuous, impairment of function is severe, and so on almost to infinity.

The minute changes that occur in a vascular tissue when it becomes the seat of inflammation as the result of the action of an irritant may be examined in the living animal. Though the frog is most commonly used for the experiment, it has been shown that the changes observed in the frog are true also for warm-blooded animals such as the dog and the rabbit. With regard to the changes that are seen in the frog in inflammation, the description given by Cohnheim is so vivid that it will be reproduced here *verbatim*. In whatever way it may be necessary to differ in the interpretation of the results from Cohnheim, there can be no hesitation in accepting the description that he gives of the changes observed as perfect. Cohnheim writes as follows[1]:—

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[1] English translation, pp. 247–253.

"You need only expose the vessels of a part to the air by removing its protective coverings; when, if you have selected a transparent tissue, there is nothing to hinder microscopic examination. The simplest method is to draw out the intestine of a curarised frog through a laterally placed opening in the abdominal wall, and to bring the mesentery under the microscope, after having carefully spread it out on a slide adapted for the purpose. Or you may wound the papillary surface of the frog's tongue by removing the papillæ with a cut of the scissors, carried parallel to the surface; a number of larger and smaller vessels will thus be exposed in the base of the wound. No further violence should be used after this; on the contrary, the more carefully you protect the preparation from all disturbing accidents, as contamination by blood, stretching, or loss of moisture, the more regularly will a succession of appearances be developed which are well calculated to fully engross your attention.

"The first thing you notice in the exposed vessels is a *dilatation*, which occurs chiefly in the arteries, then in the veins, and least of all in the capillaries. With the dilatation which is gradually developed, but which during the space of fifteen to twenty minutes has usually attained considerable proportions (often exceeding twice the original diameter), there immediately sets in in the mesentery an *acceleration of the blood-stream*, most striking again in the arteries, but very apparent in the veins and capillaries also. Yet this acceleration never lasts long; after half an hour or an hour, or sometimes after a shorter or a longer interval, it invariably gives place to a decided *retardation*, the velocity of the stream falling more or less below the normal standard, and so continuing as long as the vessels occupy their exposed situation. Such is the course of events in the mesentery experiment, in which not only the vessels of the mesentery but their terminal ramifications in the intestine are laid bare. In the wound of the tongue, on the other hand, the acceleration is often altogether absent; and *from the first there is associated with the dilatation a retardation of the stream*, which increases as the dilatation increases. This is the case, at least, when a number of larger branches are exposed in the wound but not their finer ramifications. Should the latter also be laid bare, a temporary acceleration precedes the slowing of the blood-stream, which never fails finally to set in in the exposed vessels.

"This stage having been reached, the vessels are seen to be all of them very wide; a multitude of capillaries which were formerly hardly perceptible can now be clearly distinguished; pulsation is unusually conspicuous on into the finest ramifications of the arteries; while the flow is everywhere slower than normal, so that the individual corpuscles may easily be recognised not only in the capillaries but also in the veins, and during diastole even in the arteries. In consequence of the tardy forward movement, the corpuscles accumulate in large numbers in the capillaries, so that the latter appear redder than usual, and therefore fuller, more voluminous; yet their cross-section, as just stated, is only very inconsiderably enlarged. But it is the veins rather than the capillaries that attract the notice of the observer; for slowly and gradually there is developed in them an extremely characteristic condition; *the originally plasmatic zone becomes filled with innumerable colourless corpuscles.* The plasmatic zone of the veins, you will remember, is always occupied by scattered colourless blood-corpuscles, which, owing to their globular form and low specific gravity, are driven into the periphery of the stream, and whose adhesiveness makes it difficult for them to escape from the wall once they have come into contact with it. It is obvious that this difficulty will be enhanced in proportion to the slowness of the blood-stream; and thus it is not surprising that a gradual accumulation of colourless corpuscles should take place in the peripheral zone and here come to be *comparatively* motionless. For that a state of absolute rest, an actual standstill, is out of the question, I need hardly mention expressly; the colourless cells of the plasmatic layer remain stationary at most for a time, they then advance a little, and perhaps make another short halt, and so on. Yet this does not lessen the striking contrast presented by the central column of red blood-corpuscles flowing on in an uninterrupted stream of uniform velocity and the peripheral layer of resting colourless cells; the internal surface of the vein appears paved with a single but unbroken layer of colourless corpuscles without the interposition at any time of a single red one. It is the separation of the white from the red corpuscles that gives the venous stream in these cases that characteristic appearance, anything analogous to which you will look for in vain in the other vessels. For in the capillaries, although large numbers of colourless blood-corpuscles adhere to the walls, there is always an admixture of red cells, or rather these are very decidedly in the majority. Lastly, in the arteries there is seen during diastole, almost at the moment of exit of the wave, a number of colourless corpuscles rolling straight towards the periphery; yet these are always swept into the stream at the next systole, so that the development of a resting peripheral layer is here altogether out of the question.

"But the eye of the observer hardly has time to catch all the details of the picture before it is fettered by a very unexpected occurrence. Usually it is a vein with the typical peripheral arrangement of the white corpuscles, but sometimes a capillary, that first displays the phenomenon. A pointed projection is seen on the external contour of the vessel wall; it pushes itself further outwards, increases in thickness, and the pointed projection is transformed into a colourless rounded hump; this grows longer and thicker, throws out fresh points and gradually withdraws itself from the vessel wall, with which at last it is connected only by a long thin pedicle. Finally this also detaches itself, and now there lies outside the vessel a colourless, faintly glittering, contractile corpuscle with a few short processes, and one long one, of the size of a white blood-cell, and having one or more nuclei; in a word, *a colourless blood-corpuscle.* While this is taking place at one spot, the same process has been carried on in other portions of the veins and capillaries. Quite a large number of white blood-cells have betaken themselves to the exterior of the blood-vessels and these are constantly followed by fresh ones, whose place in the peripheral layer is immediately occupied by others. Like every stage of the entire process on from the moment of exposure, these phenomena may develop either rapidly or slowly; at one time the earliest *emigration* very quickly succeeds the pavementing; at another, an hour or more may pass without anything happening to draw attention to the contour of a single vein or capillary. In any case the final result after six or eight or more hours have elapsed will be the enclosure of all the veins, small and large, of the mesentery or wound of the tongue with several layers of colourless corpuscles. These fence in the veins, in the interior of which the previously described conditions continue, namely, the peripheral arrangement of the colourless cells and the central unbroken flow of red blood-corpuscles. Nothing analogous has occurred in connection with the arteries, *their contour has remained smooth as before*, nor can a solitary corpuscle, red or white, be discovered on their outer surface, except, of course, such as may have reached them from the neighbouring veins. On the other hand, the capillaries take, as already mentioned, a very active part in the process, yet these and the capillary veins differ remarkably from the veins proper in that not merely *colourless* but *red* corpuscles emigrate from them. The result is completely in harmony with the condition of the stream in these vessels, for I have already called your attention to the fact that in the veins only white corpuscles, in the capillaries both varieties, are in contact with the vessel wall, so that whether a preponderance of white or of red corpuscles passes out of a given capillary depends solely on the numerical relations of the cells accumulated in its interior.

"Keeping pace with this *exodus*, *emigration*, or, as it is also called, *extravasation*, of corpuscular elements, there occurs an increased transudation of fluid, in consequence of which the meshes of the mesentery or the tissues of the tongue are infiltrated and swell. But this is not all. The extravasated colourless corpuscles distribute themselves, in proportion as their numbers increase, over a larger area, forsaking the neighbourhood of the vessels from which they were derived. The tissues become more and more densely packed with them, while the red cells, which have not the power of independent locomotion, remain seated in the vicinity of their capillaries, yet these also may be carried off by the stream of transudation. Soon a moment must arrive when the products of exudation and transudation can no longer be accommodated in the tissues. They now gain the free surface of the mesentery, and should the transuded fluid coagulate, as is the rule here, the final result of the processes just described will be *the deposition on the mesentery,* as well as on the intestine, *of a fibrinous pseudomembrane densely packed with colourless blood-corpuscles, and interspersed with isolated red cells.*

"The appearances are essentially the same after painting the smooth surface of the frog's tongue with *croton oil.* Of course it is absolutely necessary to employ the croton oil in extreme dilution—about one part to forty or fifty of olive oil—and even then to allow the mixture to act only a very short time. For if you do not soon wipe off the oil, or, still more, if you make use of a concentrated solution, you at once get an intense corrosive action, as evidenced by the *formation of thrombi* in the larger vessels, and the occurrence of complete *stasis* in some of the capillaries, more especially the superficial ones. The weak solution, on the other hand, provokes *an enormous dilatation of all the vessels,* which at first is accompanied by *a very great acceleration of the blood-stream.* After a time, however, the velocity commences to diminish in the dilated vessels, and is converted into a pronounced retardation of the entire circulation through the tongue. With the retardation there is simultaneously developed the peripheral arrangement of the colourless blood-corpuscles in the veins, and the accumulation of blood-corpuscles in the capillaries, which is so extreme as to result in the actual stagnation of the red cells in such of the latter as are superficially situated. And now it will not be long before extravasation from some of the capillaries and veins begins. As might be expected, the veins supply only colourless corpuscles; the capillaries, whose blood is becoming stagnant, almost exclusively red, while from those capillaries in which the flow, though retarded, is still sustained, coloured and uncoloured cells pass out together, at one point more colourless, at another more red, and these may even collect into small clumps outside the vessels. At the same time the swelling of the tongue increases, it becomes intensely reddened; a number of small punctiform hæmorrhages are already apparent even to the naked eye, while microscopic examination reveals a no less dense accumulation of colourless corpuscles throughout its tissues.

"The development of this process is still more evident and more easily observable when only a portion of the tongue and not the entire organ is corroded. The action of the caustic shades off and becomes gradually feebler towards the periphery, so that, by passing from the circumference to the centre of the injured part, one has an opportunity of examining side by side the whole of the processes which otherwise are observed to develop in succession. On microscopic examination of the frog's tongue, a circumscribed portion of which has been touched with nitrate of silver or other caustic on the previous day, you will find the vicinity of the part to which the caustic has been applied swollen, and presenting a number of almost concentric zones. At the periphery you come upon a perfectly normal circulation, then upon a zone of dilated vessels, in which the flow is retarded, but whose contour is smooth; next upon another zone of dilated vessels from which abundant extravasation is taking place—an extravasation, as invariably happens, of colourless blood-corpuscles from the capillaries and veins, and of red cells from the capillaries. Then follows still another zone in which the flow is excessively retarded and the capillaries densely packed with red corpuscles almost at rest: it is here that you meet with the most copious diapedesis of red corpuscles. To this succeeds, further inwards, and immediately surrounding the eschar, a zone of *absolute stasis,* in which the blood-vessels are mortified and their blood coagulated, and as a result, of course, all extravasation is here at an end. The last the central point of the entire series, is obviously the eschar."

We may then say that the changes seen in the tissues when they have been exposed to the action of an irritant are: I. Dilatation of vessels accompanied by acceleration of blood-flow;

II. Dilatation of vessels accompanied by retardation of blood-flow; III. Exudation; IV. Migration of leucocytes and diapedesis of red blood-corpuscles, though the latter is not invariable. These must be considered a little more in detail, but since the changes in the blood-vessels and in the flow of blood and the exudation have already been discussed at length in previous chapters, they will call for fewer remarks than migration and certain processes connected therewith.

II. **The Dilatation of Blood-Vessels.**—It is obvious that the dilatation of blood-vessels which occurs in inflammation must be directly connected with the cardinal sign of redness. A part which is inflamed is fuller of blood than it is when normal. That profuse hæmorrhage follows when an incision is made into an inflamed area has long been known to surgeons, and Cohnheim showed that the amount of blood which may be obtained in a given time from a vein in a severely inflamed limb of a dog is about double that obtained from the corresponding vein in the fellow limb. Nevertheless, in very severe cases, and especially after the inflammation has been some time in existence, the amount of blood obtained from the injured limb may be less than that obtained from the sound limb. The reason of this lies, in part, in the fact that when exudation and migration are very considerable, and when in addition marked extravasation of red blood-corpuscles is present, the extravascular material exerts so great a pressure upon the blood-vessels which it surrounds, that the flow of blood through them is impeded. The blood in an inflamed area is arterial in colour, because the rapidity with which the blood is renewed in the neighbourhood of a focus of inflammation does not allow of so great a reduction of the oxyhæmoglobin as normal; even in the veins the blood may be quite red. But this is not always the case, for if inflammation occur in a part which is the seat of venous congestion, *e.g.*, in the formation of a so-called varicose ulcer, the parts surrounding the ulcer are commonly purple and not red.

As to the method whereby the dilatation of the arteries is brought about, it is impossible to speak with certainty, but the fact that the dilatation is accompanied by increased outflow of lymph seems to indicate that we have to deal with an active hyperæmia. It is certain that the condition is not due simply to vaso-motor paralysis, for when inflammation occurs in a part the vaso-motor nerves of which are cut, the blood-vessels undergo a further dilatation. Possibly the irritant may act in an inhibitory manner on the local mechanism in the walls of the smaller arteries. Nothing is known as to the part played by the veins and the capillaries in reference to the hyperæmia. They are fuller of blood than normal, and the flow through them is increased in rapidity—at all events at first. No doubt this is due to passive distension succeeding on the arterial dilatation, but whether the arterial dilatation is the sole cause, or whether it is aided by an active dilatation of the capillaries and of the veins, it is impossible to say.

In the later stages of the dilatation, when acceleration of the stream gives place to retardation, the matter is different, for then it can be recognised that some alteration has taken place —physical or vital—in the walls of the capillaries or veins. This change, however, is of a nature which we cannot recognise by any microscopical changes in the endothelial cells short of actual rupture; it is indicated by the increased flow of concentrated lymph, and by the migration of leucocytes and diapedesis of red blood-corpuscles which are found to take place. These changes are very important, indeed Cohnheim regarded them as being the essential feature of inflammation. He considered that the retardation of blood-flow which occurs after the lapse of a certain time in the immediate neighbourhood of a focus of inflammation is certainly due to change in the vessel wall, and not to any change in the constitution of the blood. For if milk be substituted for blood as the circulating fluid, the phenomena are, *mutatis mutandis*, exactly the same, and the passage of fat globules is impeded in the vessels at the seat of inflammation no less than was previously the passage of corpuscles. According to Cohnheim, the blood-vessel wall becomes altered in that it becomes more adhesive than normal.

It is, at least, possible that a change in the vessel wall is the distal and not the proximate cause of retardation. It would seem that the margination of the leucocytes by narrowing the lumen of the vessels, and that the exuded fluid by the pressure which it exerts outside the vessels, and by the greatly increased local specific gravity of the blood which exudation produces within the vessel walls, are factors that must oppose an obstacle to the blood-flow. And this without bringing into the question the pressure that must be exerted by the numbers of migrated leucocytes. It hardly seems necessary to presuppose an increased adhesiveness of the vessel wall. It is obvious, too, that a substitution of milk for blood does not finally dispose of the question. For if the blood-vessel walls are in a condition in which they put forth more lymph than normal from blood, there is no inherent reason why they should not put forth whey from the milk which is within them. Further, even if it be granted that the vessel walls are more adhesive than normal, there is no doubt that this is not directly due to the action of the irritant. Some time elapses before retardation of the blood-flow sets in, and it might rather be assumed that the direct action of the irritant showed itself in the arterial dilatation with acceleration of blood-flow. As a matter of fact, however, even this conclusion would be incorrect, since, if great care be taken, it can be seen that the direct action of the irritant upon the vessel walls shows itself in a passing constriction, during which, of course, the blood-flow is diminished in quantity and in velocity.

III. **The Exudation.**—We have already entered at length into the pathology of œdema, and have found that inflammatory œdema must be regarded as dependent upon an increased need of the tissues for nutrition. Inflammatory exudation from the blood-vessels will therefore detain us no longer from that aspect, but it is necessary to point out that the amount of exudation is to a large extent dependent upon the mechanical conditions obtaining in the part that is the seat of inflammation. The amount of hyperæmia being also dependent upon the same conditions, they may be considered together.

(i.) **The Effect of Mechanical Conditions exemplified**

**by Inflammation of** (*a*) *Bone.*—When a bone becomes inflamed the available space in the Haversian canals which contain the blood-vessels is so small, and the walls of the canals are so rigid, that neither dilatation of blood-vessels nor exudation of fluid can take place to any extent. The bone shows no swelling, and redness, if present, is very slight. Of course this is not the case when the periosteum itself is inflamed. Then considerable swelling and redness may be present, but these two cardinal signs involve the periosteum and not the bone proper. Apart from periosteal changes, it would be almost impossible to determine whether a bone is inflamed or no. Nevertheless, there is an increased output of fluid from the blood-vessels in the Haversian canals, and it is the pressure which this fluid exerts that is the chief cause of the great pain associated with inflammation of bone. Moreover, the exudation may act in another way besides causing pain; by the obstacle which it presents to the blood-flow the circulation in the bone may be cut off to such an extent that a portion of the bone dies from lack of nutrition. Such a termination of inflammation of bone is by no means uncommon.

(*b*) *Lung.*—In the case of the lung, on the other hand, the conditions are as nearly as possible the exact converse. Here practically no impediment is placed in the way of exudation. The pneumonic inflammation caused by Fränkel's pneumococcus leads to so excessive an amount of coagulative exudation that a whole lobe, or even a whole lung, rapidly becomes converted into a solid mass, so dense that the condition is, not inappropriately, known as "hepatisation." But the exudation exerts little or no pressure upon the blood-vessels of the lungs, and hence the lung in this condition is intensely congested, while, as a further result of the same relative absence of pressure, gangrene of the lung following on a simple pneumonia is of extremely rare occurrence. Nevertheless, in persons whose vitality is greatly lowered, as for example in chronic drunkards, even the small increase of pressure exerted by the pneumonic exudation is sufficient to produce gangrene of the lung.

(*c*) *Hand.*—The hand is an example of a part where both conditions may be seen. An inflammation, otherwise of the same intensity, occurring in the dense tissues of the palmar surface, is accompanied by far less hyperæmia and swelling, far more pain, than an inflammation on the dorsal surface. Other examples of similar conditions can readily be called to mind.

(ii.) **Characters of Exudation: "False Membranes," Croupous and Diphtheritic Inflammation.**—The characters of inflammatory exudations vary considerably. This is not so much, however, because the exudation fluid itself varies greatly in composition, as because of the variation in the number and kind of the formed elements which are suspended in the fluid. It has already been said (p. 215) that inflammatory exudation is highly albuminous and that it therefore has a high specific gravity. It is commonly auto-coagulable, and this no doubt depends in part upon the large numbers of leucocytes present. When it does not coagulate, this may depend upon the presence of some substance (*e.g.*, albumoses) which restrains coagulation, or may depend upon the fact that after coagulation the fibrin has become dissolved by the action of some proteolytic ferment. A good example of the latter process is seen in the resolution of croupous pneumonia, to which reference will be made later. This process is probably of common occurrence.

When an exudation coagulates it is known as sero-fibrinous or fibrinous. A fibrinous exudation from blood-vessels which lie beneath a free surface—especially if the surface be a mucous membrane—has different characters in different cases. In one case the exudation may yield a membrane such as was described on p. 263. It can then be easily stripped off the tissue on which it lies; it removes along with it none of the subjacent mucous membrane, excepting perhaps small agglomerations of epithelial cells; it does not, therefore, leave a bleeding surface; it shows little or no tendency to re-formation once it has been removed. In another case the membranous appearance of the fibrinous material may be but little different, and yet it is stripped off the mucous surface with difficulty, leaves a bleeding surface beneath, and forms again after removal with great readiness. Histological examination shows that in the first case the fluid which has exuded from the subjacent blood-vessels has reached the surface before coagulation has set in, and that in the second case coagulation has taken place while the fluid was still lying between the cells and connective tissue which cover the inflamed blood-vessels. In accordance with the observation that coagulation of a coagulable fluid takes place more readily where the tissues with which the fluid is in contact are dead, it is found that where the coagulation takes place between the cells and connective tissue fibres of the mucous membrane, these cells and connective tissue fibres are dead. As a matter of fact they have undergone the change, to which we shall have to return later, known as coagulative necrosis. These differences in character of the membranes depend entirely upon the degree of severity with which the irritant that causes inflammation acts upon the tissues. Where the strands of fibrin intersect the proper elements of the tissues, the irritant is more severe; where the strands of fibrin are superficial the irritant is less severe. In both varieties of membrane, leucocytes are enclosed between the meshes of the fibrin network, but in the interstitial variety the leucocytes are more numerous, and commonly there are also present larger or smaller numbers of extravasated red blood-corpuscles.

Now in the neighbourhood of the pharynx and larynx two classes of case have long been known in which inflammation is accompanied by the formation of a membrane. In the one—croup—the membrane is superficial, in the other—diphtheria—the membrane is interstitial. From this fact an inflammation which leads to the formation of a superficial membrane was termed "croupous," that which leads to the formation of an interstitial membrane was termed "diphtheritic." The membranes themselves were known as "false membranes" or "pseudo-membranes." At a time when the existence of the diphtheria bacillus was not known, these differences in characters of the membranes were of great diagnostic significance, since it was found that those cases in which an interstitial "false membrane" is formed run a different course, and (apart from treatment) are attended by a far higher mortality than those in which a superficial "false membrane" is formed. At the present time, though some attention is paid to the characters of the membrane, it is known that they are frequently misleading, and in the diagnosis of diphtheria, stress is laid almost entirely upon the presence or absence of the specific bacillus of diphtheria.

So-called diphtheritic membranes are also found on the mucous membrane of the stomach, intestines, etc., and on wounds. In this country the tendency is to reserve the name "diphtheritic" for membranes occurring in cases in which the clinical signs of diphtheria, or, at the present day, diphtheria bacilli, are present, but on the Continent, and particularly in Germany, the histological features of the membrane determine the use of the word "diphtheritic" with the disadvantage that a wound may be said to be covered with a "diphtheritic membrane" when it has no association whatever with the disease caused by the diphtheria bacillus. It would simplify matters greatly if the terms "croupous" and "diphtheritic" were entirely discarded, and the characters of the "membrane" were distinguished in some other way.

Before leaving the fibrinous exudations it is necessary to state that the explanation given above as to the mode of formation of superficial or "false" membranes is not universally accepted. For example, in the case of the layer of fibrin which covers the lung in acute pleurisy, Neumann, following Grawitz and Schleiffarth, maintains that it is formed largely by a "fibrinoid" degeneration of the connective tissue lying immediately beneath the endothelial cells of the pleura. He points out that if the false membrane were formed by a deposition of fibrin from the inflammatory exudation upon the uninjured endothelium of the pleura, as is usually assumed to be the case, two conditions necessarily follow. Firstly, the endothelial cells should, in microscopic sections, be found to form an uninterrupted layer *beneath* the fibrin; secondly, in microscopic section the under surface of the layer of fibrin should form a regular line not dipping down into the lung tissue. With regard to the first point, Neumann maintains that microscopical examination of the surface of a false membrane shows that endothelial cells form a fairly complete covering for the false membrane; in other words, it shows that the membrane is formed beneath the layer of endothelial cells and not deposited upon it.[1] With regard to the second point, he finds that sections taken at right angles to the surface of the membrane show that the under surface of the membrane is not regular but highly irregular. He therefore rejects the view that such membranes are wholly formed by deposition of fibrin from the inflammatory exudation. This explanation, however, is not accepted by such competent observers as Ziegler, Orth, Marchand, and others.

The colour of inflammatory exudations varies in different cases. In an inflammation of moderate severity the fluid is commonly straw-coloured, and owing to the poorness in cells it is clear or but faintly opalescent. Where the severity is greater, the number of migrated leucocytes is commonly sufficient to cause the fluid to become definitely turbid, or to constitute pus. We shall not discuss purulent exudations here, as it will be necessary to consider pus-formation in detail later. When the inflammation leads to more than a minimal diapedesis of red blood-corpuscles, the exudation, of course, takes a more or less red colour according to the number of red corpuscles present. In the same way, when in jaundice, bile pigments are circulating in the blood, the inflammatory exudation, like non-inflammatory exudations, is of a greenish hue. When any abnormal soluble substance, such as a urate of soda in patients suffering from gout, is circulating in the blood, it is also found in inflammatory exudations. Crystals of bi-urate of soda are frequently obtained by passing a thread through a blister raised for the purpose on a gouty person: this procedure, however, is not always devoid of risk for the patient.

(iii.) **Meaning of the Exudation for the Economy.**—Though the exuded fluid in inflammation, as we have already seen, must be regarded as primarily directed to the supply of nutriment to the devitalised tissues, it is also of use in diluting any poison, bacterial or non-bacterial, that may be present at the seat of inflammation, and, as in the case of pericarditis, in separating two mutually irritating surfaces from one another. The exudation is further in a large number of cases beneficial to the economy in that it frequently possesses marked bactericidal properties; to these reference will be made later.

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[1] This cannot be recognised if, as is usual, sections are cut perpendicular to the surface of the false membrane, since the endothelial cells do not form a perfect layer over the false membrane (Neumann).

But it is not to be expected that no disadvantages should arise from the outpouring of excessive amounts of fluid. We have already mentioned that the pain of inflammation may be aggravated by exudation in some cases, just as in others it may be relieved, and that the exudation may be the ultimate cause of gangrene or necrosis of the inflamed part. But beyond these considerations, the exudations generally, non-inflammatory as well as inflammatory, are sources of danger to the economy in two ways. Firstly, the distension of the tissues in which the exuded fluid is situated, of itself lowers their already diminished vitality, and renders them more prone to succumb to small injuries. Thus the prick of a needle, which in a healthy limb would probably be followed by no after-effects of consequence, if made into the œdematous subcutaneous tissue of a patient suffering from acute renal disease, is very liable to be followed by a severe and spreading inflammation of the skin and subcutaneous tissue. Secondly, the exuded fluid is often an extremely good culture-medium for many kinds of micro-organism. After abdominal operations, for example, if careful asepsis have not been observed, the exudation poured out into the abdominal cavity as the result of the operation is liable to afford a medium in which putrefactive and other micro-organisms readily grow. The motive of exudation is the benefit of the tissues, but benefit to the tissues is not always the result of exudation.

**IV. The Cellular Elements of the Blood in a Region of Inflammation.—(i.) The Red Blood-Corpuscles.**—The red blood-corpuscles do not call for great remark. They are apparently passive agents throughout. They are squeezed through the altered vessel wall by the pressure of the blood.

Probably they pass through definite holes in the vessel wall, but whether these are stomata or not, it is impossible to say. They remain localised at the spot where they have been extruded, excepting so far as they are carried away by the stream of exudation. They undergo no changes but degenerative changes, and, as far as is known, they subserve no purpose. Their extravasation is perhaps the greatest argument for the view that in inflammation the blood-vessel walls are damaged, but it is not conclusive, as it is very common to find a large number of red blood-corpuscles in normal lymph.

(ii.) **The Colourless Corpuscles.**—But the case is different with the colourless corpuscles. They leave the blood-vessels, especially the small veins and capillaries, as do the red blood-corpuscles, but their migration appears in the main to be active and not passive. When they have left the blood-vessels they do not remain localised at one spot, but wander to distant parts, travelling by their own amœboid movements, and being carried by the stream of exudation. They undergo changes, many of which are not degenerative.

(A) **Conditions necessary for Migration of Colourless Blood-Corpuscles.**—(*a*) *Vascular Conditions.*—For the migration of leucocytes two conditions at least are necessary: (1) a circulation of blood must still be going on through the blood-vessel from which emigration is taking place; (2) the leucocytes must be in contact with the vessel wall.

With regard to the first condition, Cohnheim showed that migration of leucocytes ceases when the circulation through the vessel which is the seat of migration is stopped. In consequence of this observation he discarded the older view that migration is active, and, adopting the view put forward by Hering, argued that leucocytes are passively extruded from the vessels owing to the blood-pressure behind them. This view, however, was not universally accepted, and at the present time—as has already been said—it is generally held that leucocytes leave the blood-vessels by virtue of their own amœboid movements, though it is allowed that a circulation through the vessel is also necessary. Whether they pass through stomata, or through endothelial cells, or through the cement substance lying between the endothelial cells, is a matter of doubt.

With regard to the second condition, following Cohnheim, most authors regard the adhesion of leucocytes to the vessel wall in inflammation as evidence of a modification of the wall whereby it becomes more adhesive. But apart from the facts that retardation of the blood-flow necessarily leads to the accumulation of a greater number of the specifically lighter colourless blood-corpuscles in the plasmatic layer; that the movement of fluid in the plasmatic layer is slower than elsewhere in the blood-stream, and therefore that when leucocytes have reached the plasmatic layer, their tendency to move forwards is greatly diminished; and that contact with the vessel wall calls forth the property of living protoplasm known as "tactile sensibility," facts which in themselves are sufficient explanation of the margination of leucocytes, there is reason to believe that the behaviour of the leucocytes depends as much (if not more) upon changes induced in the leucocytes themselves as upon changes induced in the blood-vessel wall. Durham has found that under certain conditions the leucocytes in the peritoneal fluid tend to agglomerate into balls or to adhere closely to the omentum. He regards these facts as evidence of an increased "stickiness" of the leucocytes. But whether the leucocytes become more "sticky" or no, there is evidence that the movements of leucocytes are influenced by the presence of chemical substances in their neighbourhood. This evidence must now be considered.

(*b*) *Chemiotaxis.*—It was noticed by Engelmann, when investigating oxygen excretion by lower vegetable organisms, that various motile bacteria can be used as a test for oxygen, in that, when the organism under investigation excretes a bubble of oxygen in the fluid in which it is suspended, the bacteria also present in that fluid rapidly move towards the bubble. This formed the basis of a series of observations, made at first only by botanists, on the attractions between motile organisms and various chemical substances. It was shown by de Bary that vegetable plasmodia placed on a surface where there is little or no nutritive material move towards nutrient material if that be placed on the surface at a little distance from the plasmodium. Pfeffer and others investigated the subject still further, and it was found after examination of many chemical substances that the phenomena may be divided into three classes: (1) a class in which no movement of the plasmodium or other vegetable organism takes place; (2) a class in which the plasmodium moves towards the chemical substance; (3) a class in which the plasmodium recedes from the chemical substance. The first class does not interest us; to the phenomena of the second class Pfeffer gave the name "positive chemiotaxis"; to the phenomena of the third class he gave the name "negative chemiotaxis."

The matter was then taken up by bacteriologists, and amongst others by Gabritchewsky. Gabritchewsky saw that in chemiotaxis might lie the reason why in inflammation there is an agglomeration of leucocytes at the focus of irritation—or rather, taking a broader view, he regarded his work on chemiotaxis as filling a gap in Metchnikoff's phagocytic theory of inflammation and immunity. He made a series of observations, by which he showed that ten per cent. solutions of sodium and potassium salts, that lactic acid, quinine, alcohol, chloroform, etc., are negatively chemiotactic to leucocytes; that sterilised and non-sterilised cultures of various pathogenetic and non-pathogenetic micro-organisms are positively chemiotactic to leucocytes. Buchner advanced the matter in that he showed that the positively chemiotactic properties of various bacteria lie in proteid substances that can be separated from the bacteria. Goldscheider and Jacob made carbol-glycerine extracts of certain animal organs and found that they also are positively chemiotactic. Their work was confirmed and extended by Bloch.

As to the method whereby chemiotaxis is brought about, we are completely ignorant. Apparently the chemical substance must be to a certain extent soluble, though that solubility need not be great, since positive chemiotaxis occurs when particles of sterile metallic copper are placed in the anterior chamber of the eye. Whether the process is a physical one and is akin to diffusion and osmosis, or whether it is vital, it is, at present, impossible to say.

Not a few observers who accept the existence of positive chemiotaxis find it difficult to accept the doctrine of negative chemiotaxis. They admit that chemical substances may definitely paralyse the leucocytes, and therefore that positive chemiotaxis may be absent, but that an actual repulsion of leucocytes can take place they regard as not conclusively proved. The mere fact that leucocytes are not found in a capillary tube which has been filled with some chemical substance and inserted beneath the skin of an animal or into its abdominal cavity, does not even prove that leucocytes never entered the tube, for they might have entered and have been there dissolved; much less does such an experiment prove that leucocytes receded from the capillary tube.

There is a growing tendency to believe that the presence of leucocytes at the seat of an inflammation depends upon processes similar to those observed in positive chemiotaxis. When it is borne in mind that bacteria are perhaps the commonest cause of inflammation, and that in every inflammation, bacterial and non-bacterial, there are present at the focus of inflammation greater or less amounts of the products of tissue disorganisation, it must be admitted that chemiotaxis forms a very plausible hypothesis.

The leucocytes which leave the blood-vessels in inflammation are almost exclusively of the finely granular oxyphil type, but some of the other varieties of hæmal wandering cell migrate also. After leaving the vessel they all travel rapidly towards the seat of irritation and are joined on their way by wandering cells of the cœlomic type derived from other sources. There is reason to believe also that multiplication of the cells takes place in some degree after they have left the blood-vessels. That proliferation of cœlomic wandering cells occurs *in situ* there is no doubt.

The kind of wandering cell that predominates at the focus of inflammation depends upon a number of circumstances concerning which but little is known. The chief of these seem to be as follows: (1) the nature of the irritant; (2) the seat of the irritant; (3) the length of time during which inflammation has been in existence; (4) the species of animal used for experiment. Speaking generally, it may be said that the cells which are earliest found at the seat of irritation are oxyphil, and sometimes they are of the coarsely granular type, sometimes of the finely granular type. Hyaline cells appear at the focus of inflammation later, but if the irritant be very mild, they may be practically the only cell present at any time. Kanthack and Hardy hold that the predominance of finely or of coarsely granular oxyphil cells depends essentially upon whether the blood-vessels are largely involved in the inflammatory process or no. Thus they found that when a cutaneous blister is raised by means of blistering fluid (man), the cells in the exudation are mainly of the finely granular or hæmal oxyphil type, whereas when the peritoneum is the seat of irritation, produced, for example, by injection of a living culture of anthrax bacilli (rat), the cells present in the peritoneal exudation are mainly of the coarsely granular or cœlomic oxyphil type. In the frog also they found that injection of a living culture of anthrax bacilli into the dorsal lymph-sac is rapidly followed by a great increase in the number of coarsely granular oxyphil cells in the lymph. Durham was unable to confirm the latter statement, but the author's experience agrees with that of Kanthack and Hardy. As the result of injecting various kinds of micro-organism into the peritoneal cavity of guinea-pigs, Durham found that the newly-arrived cells in the peritoneal fluid that were first noticed were finely granular oxyphil cells and hyaline cells (macrophages) of various kinds. It is almost certain that the different results obtained by Kanthack and Hardy and Durham depend upon the different conditions under which these observers worked. Though little is known concerning the parts played by different varieties of wandering cell, there is no doubt that a hard and fast line cannot be laid down at present. In particular it is uncertain how far one variety of wandering cell in one animal may discharge functions carried out by another variety of wandering cell in another animal.

(B) **Phagocytosis.**—Leaving on one side the more doubtful functions of wandering cells until we come to deal with the subject of immunity, one function of the wandering cell must be mentioned which has long been recognised. It was known long before varieties of wandering cell were distinguished that leucocytes have the power of englobing particles. The process is exactly similar to that which occurs in the case of Amœba. When an amœba meets with a solid particle it puts forth a pseudopodium and gradually encloses the mass. If the particle be digestible, the amœba forms round it a vacuole, and in this vacuole the particle is broken up and digested.[1] If, on the other hand, the particle is non-digestible, as a rule, no vacuole is formed, but after a longer or shorter sojourn in the animal the particle is extruded—or, rather, the amœba flows away from the particle and leaves it behind.

So far as this function is concerned, leucocytes are exactly similar to amœbæ, and in them granules of glycogen, fat globules, carbon particles, etc., may be found normally. If carmine or indian-ink be injected into the circulation, particles of these substances are taken up by the leucocytes with great avidity. The author found, twenty minutes after injecting 50 c.c. of a thick suspension of indian-ink into the circulation of a dog weighing 6 kilos., that very few carbon particles were recognisable in the blood, but that, in the spleen particularly, the leucocytes were deeply pigmented. And it may generally be said that leucocytes have the power of englobing any small and innocuous particles with which they come into contact. If these particles can be digested they are surrounded by a vacuole and are digested; if they cannot be digested, they are held within the body of the leucocyte for a longer or shorter time. When the particles presented to the leucocytes are injurious, as for example in the case of virulent micro-organisms, the course followed by the leucocytes is, perhaps, different. This, however, is a debated point, and is bound up with the question of negative chemiotaxis. Both points will be considered later.

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[1] Le Dantec, working upon the subject of intra-cellular digestion, came to the conclusions that there is always secretion of acid into the vacuoles which amœbæ form round ingested particles, and that ingesta of all kinds are bathed with an acid fluid. Misses Greenwood and Saunders, from experiments on various protozoa, confirmed le Dantec's results, and in addition found that the mere outpouring of acid is unaccompanied by any digestive change on nutritive matter ; ingesta may be stored for many hours before they are dissolved, or digestion may follow rapidly on ingestion. Nevertheless the formation of a digestive vacuole is preceded by development of the acid reaction and is followed by its diminution. Although the secretion of acid is excited by all ingesta, the true digestive vacuole is only formed under the stimulus supplied by nutritive matter. It has not yet been shown that these results may be directly applied to the leucocytes.

To this property of leucocytes Metchnikoff gave the name "phagocytosis."

Whether in the case of leucocytes the property is directed towards nutrition it is difficult to say. There seems to be no selection on the part of the cell as to whether it shall take up digestible or non-digestible particles when both are presented to it. Kanthack and Hardy give, in a table at the end of their paper on the "Wandering Cells in Mammalia," details of an experiment in which bacilli (*B. pyocyaneus*) and indian-ink were injected into a rat. From that table it is seen that as many phagocytes attacked the bacilli which could be digested as attacked the indian-ink particles which could not. We shall see later that there is evidence that phagocytes may distinguish between varieties of bacilli, but that is a different matter. Against the nutritional view is the further fact that leucocytes are suspended in a nutritious albuminous fluid (plasma or lymph); one would expect under these circumstances that the cells should take up their nutriment from that fluid in a liquid form rather than in a solid form. It has been suggested that the phagocytic function is rather of a "scavenging" kind, and there is really no valid argument against this view, excepting the fact that in allied organisms the property is distinctly nutritive. But in estimating the value of this objection the difference in constitution of the liquid media in which the two kinds of protoplasmic cell flourish must be taken into account.

All kinds of wandering cell do not possess this property of phagocytosis to the same degree. The finely granular oxyphil cell and the hyaline cell (hæmal and cœlomic) are intensely phagocytic. Young connective tissue cells (fibroblasts) and endothelial cells of blood-vessels, and, perhaps, of lymphatics, show marked phagocytic properties, especially when they are proliferating rapidly. Giant cells are sometimes phagocytic. Lymphocytes, on the other hand, are apparently never phagocytic, and it is probable that coarsely granular oxyphil cells are non-phagocytic also. Upon this latter point, however, there is some difference of opinion.

This difference of opinion is bound up with the question as to the nature of the granules in these cells. By the greater number of authors they are considered to be "paraplastic," that is, formed at the expense of the cell-protoplasm, and, in fact, as being of the nature of secretion products. We shall see later that upon this view has been built one of the numerous theories of immunity, but it is only necessary here to remark that Metchnikoff and some of his pupils have shown that an appearance somewhat similar to that of a coarsely granular oxyphil cell may be produced by a phagocyte when the material which it has ingested has broken up into granules. Metchnikoff, in the case of *V. choleræ asiaticæ*, Cantacazène, in the case of *V. Metchnikovi*, Mesnil, in the case of *B. anthracis*, Bordet, in the case of *B. coli*, *B. typhosus*, staphylococci, streptococci, etc., describe a change in the staining reactions of micro-organisms after they have been taken up by phagocytes. At first the micro-organisms stain only with basic dyes, but as the result of phagocytic action they come at last to refuse basic dyes, and to take up acid dyes with avidity. If, then, the phagocyte be filled with broken-down particles of bacteria, and these particles stain readily with eosin, an appearance is given that can be almost indistinguishable from that yielded by a coarsely granular oxyphil cell. These observers, therefore, maintain that the granules of the coarsely granular oxyphil cell are not paraplastic, and Mesnil even goes so far as to suggest that coarsely granular oxyphil cells are simply phagocytes replete with the altered *débris* of the substances which they have ingested. Taking the coarsely granular oxyphil cell, however, as one finds it, there is less difference of opinion. It is allowed on all hands that phagocytosis by this variety of cell is uncommon; the only question is whether it ever occurs. Kanthack and Hardy with most authors maintain that coarsely granular oxyphil cells (frog, rat, guinea-pig) are never phagocytic. Mesnil holds the contrary view (lizard), and Durham (guinea-pig) found in a hanging-drop preparation one undoubted example of a coarsely granular oxyphil cell which contained an ingested bacillus (*B. megatherium*) within a vacuole.

**V. Tissue Changes in a Region of Inflammation.**—Beside the effects which an irritant produces upon blood-vessels, the proper elements of the part in which inflammation is taking place also undergo changes. It is evident that the blood-vessels cannot be affected alone, though, if the irritant be carried to the part in the blood-stream, it is possible that the vessels may suffer first and to the greatest extent. The effects of the inflammation upon the tissue elements may be divided into two classes: (1) the direct effects of the irritant; (2) the effects produced by the exudation and migration that take place from the inflamed blood-vessels. Both classes conjoin to produce that "impairment of function" which is the fifth cardinal sign of inflammation.

In the case of the tissues there is the great difficulty that one has to separate the changes which are strictly due to the action of the irritant and to the pressure of the exuded fluid and cells, from the changes which are strictly due to the increased amount of nutriment which that exuded fluid brings to the tissue elements. That is to say, in the tissue elements two sets of changes are to be observed, the one degenerative, the other proliferative. It is principally over this part of the subject that there is divergence of opinion, and it is because these two sets of processes are going on apparently at the same time that so much difficulty has been felt in attempting to frame a definition of inflammation, and the definition of one author is not accepted by another author. To this matter we shall have to return when endeavouring to form a conception of the meaning of inflammation, but it must be stated here that under inflammation the degenerative processes of the tissue elements will alone be considered. In the author's opinion, the proliferative changes are no part of inflammation, but are a part of repair. And though it is granted that degenerative and proliferative changes are in most cases of inflammation closely bound up with one another, just as, normally, cellular death and cellular proliferation are closely bound up with one another, yet the author believes that proliferative changes are only brought about because degenerative changes have occurred earlier: an inflammation may present no proliferative changes, but it must, without exception, present degenerative changes.

That degenerative changes occur in inflammation can readily be seen on examination of a microscopic section of any part in which inflammation has been going on. Thus if a section of the abdominal wall of an animal which has succumbed after two or three days to intra-peritoneal injection of a micro-organism be examined, it will be noticed that the voluntary muscle has to a large extent lost its striation and has become cloudy and granular. This change is invariable, but the muscle may also show the presence of fat globules or may have undergone the change known as Zenker's or vitreous degeneration. The cohesion of the several muscular bundles has to a large extent become dissolved, and instead of forming a compact mass, as is normally the case, the bundles separate from one another and break into more or less irregular masses. This is due to the change undergone by the connective tissue throughout the part, which has swelled up and has become more hyaline or more translucent, or in parts has completely disappeared. *Mutatis mutandis*, the same is true of any other tissue.

In those organs where the essential elements of the part normally bear a high proportion to the amount of connective tissue present, not only is the impairment of function proportionately great, but also the characters of the inflammation are of a somewhat peculiar type. For since blood-vessels other than capillaries are only found in connective tissue, the vascular changes in organs of this description are small compared with the degenerative changes undergone by the essential elements of the part. In acute hepatitis, for example, vascular changes may be, on microscopic examination of a section, quite inconspicuous, while degeneration of liver cells is extensive, and even macroscopically and during life great disorganisation of the liver may co-exist, as the result of the action of a severe irritant, with a comparatively small amount of congestion, etc. The same is true in the brain; indeed here the blood-vessels bear so small a proportion to the amount of nerve-matter, that the existence of an inflammation of the brain-substance—as apart from the meninges—has been denied by some authors.

Those forms of inflammation in which the action of the irritant is principally evident in changes in the essential cells of an organ are sometimes called "parenchymatous," in contradistinction to the "interstitial" forms of inflammation in which the connective tissue of the part is affected to the greatest extent. The distinction, however, is a bad one, for in every inflammation both essential cells and connective tissue must of necessity be involved; and, in addition, it is doubtful whether the so-called cases of pure "interstitial inflammation" are to be considered as examples of inflammation at all. This latter point will be discussed hereafter.

VI. **Causes of Variation in the Type of Inflammation.**—We must conclude, then, that in every inflammation vascular changes and tissue changes occur, but from the variability of these changes the characters of inflammation may vary in an infinitude of ways. Some of these have already been mentioned, but variations in the type of inflammation must be discussed from the broader aspect of being the products of two main factors, (1) the irritant, and (2) the tissue on which the irritant is acting.

(i.) **The Irritant.**—Irritants may vary in nature or may vary in strength, or may vary both in nature and in strength. With regard to the nature of irritants, we may conveniently distinguish organised irritants from unorganised irritants, not because there is any essential difference in the processes called forth in the two cases, but because, speaking broadly, when the irritant is organised, the wandering cells play a more prominent part than when the irritant is unorganised.

(*a*) *Effect of the* Nature *of Irritant upon Inflammation.*—In the vast majority of cases organised irritants are of a vegetable nature, whether bacillus, micrococcus, or mould, but they may be animal, such as the intestinal and superficial parasites of various kinds, hydatids, *Trichina spiralis*, chigoe, etc.[1] The unorganised irritants are of the widest variety. In one case it may be an acid, in another a wound; at one time a piece of metal, at another time excessive muscular movement; at one time it may be light, at another time heat or cold; at one time a bacterial toxin, at another time the poison of an insect; and so on. Indeed it is quite impossible to classify the varieties of unorganised irritant, but they all agree in that they are theoretically "aseptic" and that they induce the vascular and tissue changes that have been described above. Though unorganised irritants are theoretically aseptic, in not a small number of cases they, practically, are septic. A wound is a strictly unorganised irritant only when strictly aseptic, and the difficulty of preventing bacteria from playing a part in any inflammation which involves the skin or which is exposed to the air is so great, that the bulk of inflammatory conditions *as we see them* are due rather to the organised than to the unorganised irritants.

If we take an irritant of mean intensity from either class it will be seen that there is considerable macroscopic difference between the forms of inflammation that are produced. For example, the great exudation that comes on in perhaps ten minutes and is accompanied by the migration of but few leucocytes when heat raises a blister on the back of the hand, is in marked contrast with the enormous migration of leucocytes and the smaller amount of exudation that occurs in perhaps twenty-four hours when the irritant is *Staphylococcus pyogenes aureus* acting in the same region.

But though it may broadly be stated that when the irritant is unorganised, exudation is most obvious, whereas when the irritant is organised the presence of numbers of cells at the part is most obvious, this statement is not absolutely correct. For the inflammations caused by even closely allied irritants at times differ very considerably. Thus Uschinsky, investigating the action of cold upon the skin of the guinea-pig, showed that freezing by means of the ether spray for two to three minutes leads to an inflammation which is at its height 24–36 hours later, is accompanied by an excessive migration of leucocytes and is remarkable for its dryness. Heat, on the other hand, applied for the same length of time, leads to excessive exudation that is earlier at its height and is accompanied by migration of few leucocytes. Moreover the vitality of all tissues is less interfered with by cold than by heat, so that, for the production of a given degree of injury or of local death, cold must be more intense and must act for a greater length of time than heat. So, too, we shall see in the case of inflammation caused by bacteria, that some forms are associated rather with the presence of much exudation than of many cells.

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[1] The hæmatozoa, such as *Filaria sanguinis hominis*, the malaria parasites, etc., do not cause inflammation, though they lead to blood changes.

Another difference between the inflammations caused by organised and by unorganised irritants consists in the fact, that inflammation resulting from the action of a purely unorganised irritant is always strictly localised to the immediate neighbourhood of the spot on which the irritant has acted, whereas when the irritant is organised the inflammation not infrequently "spreads." This obviously depends upon the fact that the organised irritant is living and capable of multiplication, whereas the unorganised irritant is not.

(*b*) *Effect of* Intensity *of Irritant upon Inflammation.*—But if the nature of the irritant is important in determining the character of an inflammation, the strength of the irritant is no less important. If it be slight the changes which it induces may rather be regarded as the result of a stimulus than of an irritant and may be considered physiological rather than pathological. Thus, the action of heat may be such that the vascular changes induced are only those characteristic of a simple active hyperæmia; or, on the other hand, it may kill the tissue outright and then no inflammatory changes supervene except at a distance from the seat of irritation, where the action of the irritant has been less severe and has not killed the tissues. Between these extremes lie numberless intermediate conditions. The question of time also comes in, for a slight irritant long-continued may produce as great effects as a more severe irritant whose action is less prolonged.

The same is also true when the irritant is organised. A micro-organism such as *Streptococcus pyogenes* may produce vastly different forms of inflammation when inoculated into the subcutaneous tissue. If of a very low degree of virulence its effects may be limited to the production of perhaps nothing more than a slight local redness; if more virulent it may lead to the exudation of a small amount of fluid or perhaps the formation of a pustule or abscess; while if intensely virulent the inflammation may lead to the exudation of much blood-stained sero-purulent fluid into the subcutaneous tissue, and the inflammation may spread so rapidly, that in the course of a few hours a whole limb may be involved or even, by a general infection, the death of the subject may have been brought about.

(ii.) **The Tissue on which the Irritant acts.**—(*a*) *Effect of Nature of Tissue.*—The tissue upon which the irritant acts is also concerned in determining the course of inflammation. Quite apart from its density or looseness—the effect of which has already been indicated—its vascularity or comparative avascularity is of importance, for upon this depends not only the amount of exudation and the number of cells that migrate, but also to a large extent the amount of degenerative change to which the irritant gives rise. The more *vascular* a part, the less likely is an irritant to produce necrotic change and *vice versa.* Yet this last statement needs qualification, for when an irritant such as *Staphylococcus pyogenes aureus* acts upon the highly vascular liver or kidney, as in the case of septic embolism in these organs, the disorganisation of tissue to which it leads is far greater than it would be were the less vascular subcutaneous connective tissue the seat of the embolism. The *nature* of the tissue upon which the irritant acts is of importance, as well as the freedom of its blood-supply, and the delicate liver cell or kidney epithelial cell in the one case succumbs more easily than the connective tissue fibres in the other. That the course of inflammation is also modified by any general condition which modifies the *vitality* of the tissues is shown by the fact that in diabetic, albuminuric, and in alcoholic patients, inflammations run a far more severe course than they run in healthy individuals.

(*b*) *Effect of Mechanical Conditions.*—There is scarcely need to point out that mechanical conditions influence the course and duration of an inflammation. Rest and movement in particular are of importance in this connection. Thus an irritant which, acting on the skin on the back of the hand over the shaft of a metacarpal bone, would produce an insignificant pustule, may, if situated over the metacarpo-phalangeal joint, produce an ulcer extending into and disorganising the joint. The different result is due solely to the movement of the joint, for if the part be kept at complete rest the inflammation runs the same course in the two cases.

(*c*) *Effect of Integrity or Otherwise of Nervous Supply.*—The integrity or otherwise of the nervous supply to a part is of great importance in determining the course which shall be run by a given inflammation. This can readily be seen in the following experiment devised by Samuel to illustrate the point. Three rabbits, A, B and C, are taken, and in A the sympathetic nerve to the ear is cut on the right side, in B the sympathetic nerve is cut on the right side, and the greater and lesser auricular nerves (sensory) are cut on the left side, while C is kept as a control. Both ears of each rabbit are then exposed for three minutes to water at 54° C. It will be found that the subsequent inflammation runs the quickest and best course in C; that it is more severe and lasts longer, but ends favourably in A; and that in B it runs a lingering and unfavourable course, accompanied in most cases by gangrene of the heated part of the left ear. It is obvious from this experiment that section of the vaso-constrictors with hyperæmia influences the inflammation unfavourably, that vaso-constriction (in the left ear of A, and compensatory to the hyperæmia in the right ear) and anæmia influence the course of inflammation unfavourably, and that vaso-constriction and anæmia, when conjoined with loss of sensation (left ear of B), cause the inflammation to run an extremely severe course.

That loss of sensation in a part is particularly associated with severe inflammation has long been known. Without entering into a discussion of the question concerning "trophic" nerves, mention may be made of the well-known facts that section of the ophthalmic branch of the fifth nerve is followed under ordinary circumstances by severe ulceration of the cornea, and that in patients whose spinal cord or brain has been injured, pressure or other feeble irritants readily cause inflammatory conditions of a particularly severe type—the so-called acute bedsores. In the case of the eye it is taught that the inflammatory condition is essentially due to the fact that the anæsthetic conjunctiva does not guard against injury, and there is no doubt that if the eye be carefully protected from irritants, such as dust, etc., inflammation does not occur. Samuel's experiment, too, *apparently* shows us that the *same* irritant produces far greater effects in an anæsthetic part than it does in a part under identical conditions, with the exception of loss of sensation. But it is reasonable to suppose that the two ears of B, so far as irritant is concerned, are not in the same condition, for the animal would guard the sentient ear against further injury, but owing to lack of sensation would not protect the other ear against accessory irritants. On the whole, however, it is probable that in some unknown way the course taken by an inflammation is controlled by the nervous system.

In favour of this view is also the fact that in certain individuals hypnotic suggestion may lead to the appearance of definite inflammatory conditions, apart from the action of an irritant. Experiments of this kind must be received with extreme caution, but there is no doubt that in suitable persons the hypnotic suggestion that a given substance applied to the skin is red hot, whereas actually it is at room-temperature, produces inflammatory conditions, including the formation of a blister at the seat of application, which cannot be distinguished from the conditions that would be produced in the normal subject if the given substance had in reality been red hot.

Processes going on in one part of the body also affect the course of inflammation in another part of the body. Samuel shows that the inflammation which commonly appears after application of croton oil to a rabbit's ear, or after scalding, completely fails if the other ear be immersed for several hours after application of the irritant in water at 15° C. This is not due to reflex action of the ordinary kind, for the same result obtains if a leg be immersed in water at 15° C. instead of an ear, nor does it depend upon cooling of the blood, for, on the contrary, the temperature of the blood rises somewhat under such conditions. Samuel finds himself completely unable to explain this experiment, and perhaps it is no help to regard it as dependent upon some obscure nerve action. A somewhat similar difficulty occurs in the case of rabbits A and B mentioned above. It is not clear why the right ears of the two animals should not run the same inflammatory course, and yet the right ear of B, in which the sensory nerves of the left ear are cut, runs a distinctly less favourable course. Possibly we are here on the outskirts of a problem which has a wide-reaching therapeutic importance.

We see, then, that when an irritant acts upon a living tissue it invariably produces the following results:—

1. Degenerative changes involving the tissue elements.
2. Vascular changes showing themselves by hyperæmia and exudation.
3. Migration of wandering cells.

All of these conditions are present, though they do not bear the same ratios to one another in all cases.

But inflammation is not a condition of equilibrium. No sooner has it become developed than other changes supervene. These changes are of two kinds, physiological, if the irritant ceases to act, pathological, if the irritant continues to act. These sequels to inflammation will be considered in the following chapter.

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# CHAPTER VIII.

## THE SEQUELS OF INFLAMMATION.

*Synopsis.*

- I. General Considerations. The Physiological and Pathological Sequels of Inflammation.
- II. Resolution.
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**I. General Considerations.**—If we consider the phenomena which occur under normal physiological conditions in a gland whose nerve has been stimulated, we find, when nerve-stimulation ceases, that the gland commences to return to a resting state, the hyperæmia disappears, secretion is no longer poured out, and the work done by the gland-cells is directed not to the formation of a secretion, but to their own re-establishment and to the storage within themselves of the products of protoplasmic activity. In other words, secretion is followed by a return to normal, including therewith a replacement of those cells which had broken down under stimulation to form the secretion.

Now, though the cases are not absolutely analogous, the changes that succeed on the cessation of irritant action in inflammation and on the cessation of nerve action in secretion have many points in common. For when the irritant ceases to act, inflammation commences to subside and repair of defects caused by the action of the irritant commences to take place. That is to say, resolution and repair—the physiological sequels of inflammation—have their counterparts in the physiological sequels of a normal glandular secretion.

Resolution and repair are invariably associated with one another. For since inflammation is always associated with degenerative changes in the tissue cells, with hyperæmia and exudation, and with migration of wandering cells, when inflammation ceases there is always need for the removal of degenerative products and the subsidence of the other excessive conditions, as well as for the repair of those defects to which the degenerative changes in the tissue elements have given rise.

It is obvious that the amount of repair that is necessary depends upon the degree to which degenerative tissue changes have entered into the inflammation, and, therefore, that repair may be a prominent or an insignificant part of the sequels. In some cases the degenerative tissue changes are of so little importance that the phenomena which combine to make up "resolution" can be studied independently: such is the resolution of acute lobar pneumonia. In other cases, removal of tissue, whether by the knife or as the result of degenerative change, has been so great that reparative processes are well-marked: such is the repair or the healing of a wound.

**II. Resolution.—(i.) Primary and Subordinate Irritants.**—Before proceeding to examine resolution and repair more closely it must be pointed out that the action of an irritant is really a more complex matter than appears at first sight. If, under perfectly aseptic conditions, an incision be made into the skin, the action of the irritant is not confined to the time occupied by the actual incision but lasts for a longer period. For the cells that have been damaged by the knife, the blood that has been effused, the inflammatory exudation that is poured out, all take up and carry on the work of irritation in their turn. The inflammation, therefore, that follows is the total result produced by the actions of the primary irritant and of the multitudinous subordinate irritants to which the incision or primary irritant has given rise. It is because of the existence of these subordinate irritants that inflammations persist and become chronic.

Now, since irritant action must be regarded as dependent upon both primary and subordinate irritants, and since the total results of irritant action are summed up in the term "inflammation," it follows that the *physiological sequels* of inflammation cannot take place so long as these subordinate irritants continue to act, but that, on the other hand, inflammation must persist. Before resolution and repair can take place, the degenerated tissue elements, the effused blood, the excess of exudation over that which is necessary for proper nutrition of the tissues must cease to act as irritants. In some cases this end is attained very simply. In the inflammation that follows upon the sting of a bee, degenerative changes are minute, and the irritant afforded by the copious exudation, after exudation has done its work of diluting the primary irritant, is removed by a drainage of the œdematous tissue spaces into the lymphatics. The case of acute lobar pneumonia is similar but not quite so simple. The pneumococcus leads to a very considerable hyperæmia and exudation, and the exudation, in some manner with which we are not at present concerned, kills the micro-organism and neutralises its poison. The primary irritant is therefore overcome, but the secondary irritant, represented in the main by the coagulated exudation, persists, and of itself keeps up the inflammation until such time as it has become liquefied and has been removed by the lymphatics, by the blood-vessels, and by expectoration. Hence in pneumonia, resolution and repair do not set in so soon as in the other case. Those cases of acute lobar pneumonia in which this maintenance of irritation is inordinately prolonged, owing to failure or delay in the liquefaction of the coagulated exudation, are liable to terminate in abscess, gangrene, etc., of the lung; in other words, in them, the sequels of the inflammation are not physiological but are pathological.

Resolution of an inflammation is therefore synonymous with removal of the results of irritant action. In inflammation the blood-vessels become dilated and the blood-flow is retarded or accelerated according to circumstances, in resolution the blood-vessels are contracted towards normal and the blood-flow is accelerated or retarded according to circumstances; in inflammation exudation from the blood-vessels is greater than the amount of fluid that drains away by the lymphatics, in resolution the amount of fluid that flows away by the lymphatics is greater than the amount of fluid that leaves the blood-vessels; in inflammation cells leave the blood-vessels and wander towards the focus of irritation, in resolution emigration ceases and such leucocytes as are already at the focus of irritation wander away or are carried away in the lymph-stream; in inflammation the sensibility and temperature of the part increase, in resolution they diminish again towards the normal; in inflammation tissue elements are disorganised or are destroyed, in resolution the dead tissue elements are removed, and those elements whose vitality has not been lowered to too great an extent recover.

It is not necessary to discuss the phenomena of resolution in detail, for the processes that are at work are, in the main, the converse of those which lead up to the phenomena of inflammation, but a few remarks are necessary upon the methods whereby irritant action is arrested.

(ii.) **Arrest of Irritant Action.**—We have already spoken of the means whereby the action of certain subordinate irritants is abolished, but no mention has been made of the means whereby the action of the primary irritant is arrested. In this connection all consideration of organised irritants will be omitted, as the manner in which the cells and the fluids of the body deal with bacteria must be discussed in full in a later chapter. But in the case of unorganised irritants the matter is simpler and may conveniently be considered here.

The process differs somewhat according to the nature of the irritant in question, but the means whereby the end is attained almost invariably consists essentially in the exudation of a coagulable fluid and the migration and proliferation of wandering cells.

(*a*) *Dilution.*—Without entering at present into the question whether the phenomena of inflammation are purposeful or no, there can be no doubt, for example, that the irritant action of liquor epispasticus applied to the surface of the body is arrested or diminished by the output of that large quantity of fluid which characterises inflammation caused by this agent. So, too, the exudation which takes place into the peritoneal cavity whenever a concentrated solution is injected into it, dilutes that solution and renders it less irritating; and the exudation poured out into the bronchi after an irritating gas has been inhaled, protects the epithelium from the further action of that gas. But the exudation does not only arrest or diminish the action of irritants in these ways, it may also coagulate, and, to a large extent, localise the irritant. It is by no means rare to find a collection of inflammatory material in the pleural or the peritoneal cavity shut off from the main cavity by a layer of fibrin; and the wall of an acute abscess really constitutes a barrier—largely composed of coagulated exudation—against the extension of the irritant which called forth the inflammation.

(*b*) *Removal.*—When the irritant is solid, and in particular when it is insoluble in the slightly alkaline, saline, and albuminous lymph, it acts in a mechanical manner, and its action is diminished or arrested in other ways. If it is of such a kind that it can be broken up by phagocytes, it gradually becomes removed by these cells. It has been shown by Knud Faber that small masses of agar-agar impregnated with carmine particles are thus broken up and removed, phagocytic cells being found which enclose particles of the impregnated substance. When such a substance as ivory or bone is the irritant it is removed (in whole or in part) also by phagocytic action; the acid reaction which is developed in protozoa as the result of contact with foreign particles renders solution of the calcareous matrix intelligible, and the organic matrix of these substances is susceptible of peptonisation.

There is no difficulty in understanding how the removal of small particles of bone or ivory from the chief mass can be brought about, but though it is certain that the chief mass of agar-agar is slowly broken up, the steps which precede englobation by leucocytes are quite unknown. Agar-agar cannot be peptonised, and exposure to a temperature of 100° C. is the only known method whereby solid agar-agar can be liquefied. For the same reason the ultimate fate of the masses of agar-agar within the cells is equally unknown, but the fact that granules of pigment are found free in the cells shows that in some manner the agar-agar becomes dissolved.

(*c*) *Encapsulation.*—If an irritant be completely insoluble, and therefore only act mechanically, it is very common for its action to be arrested by the process known as "encapsulation." When encapsulation is complete, the foreign body is surrounded by a definite capsule of fibrous tissue, which is formed by a process identical with that which constitutes repair. But at an early stage movement of the foreign body may be hindered only by fibrin formed in the inflammatory exudation, etc., in which the foreign body lies. Sometimes, however, no recognisable change of any kind is produced; after injection of powdered glass into the pleural cavity of a guinea-pig under strict aseptic conditions, this is not infrequently the case, and in particular the absence of discoverable inflammatory phenomena is remarkable.[1] A fibrous capsule is also sometimes formed around a mass of degenerated tissue when that mass is large and aseptic. Non-malignant tumours situated in the depth of an organ are always surrounded by a fibrous capsule of greater or lesser density. When the irritant is an animal parasite (hydatid, *Trichina spiralis*), it is often encapsuled, and by deposition of calcium salts in the fibrous capsule it may ultimately become enclosed in a calcareous case.

(*d*) *Solution.*—In the case of certain irritants solidity is a relative term, and solubility or insolubility depends upon circumstances. A living amœba may be called a solid body, and it maintains its identity in the fluid in which it is suspended, but the same amœba when dead dissolves readily in the same fluid. It is highly possible that the action of solid irritants of this kind, whether primary, such as bacteria, or subordinate, such as leucocytes, is in part arrested or diminished after death of the organism by a direct solution in the exudation fluid.

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[1] Observations by Drs J. Lorrain Smith and E. G. Trevethick (Report, Brit. Assoc. for Adv. of Sci., 1894).

(*e*) *Other Methods.*—There is reason to believe, further, that the pain, the increase of temperature, the impairment of function, which accompany inflammation are also at times means whereby the action of irritants is arrested or diminished, though at the same time it must not be forgotten that these same factors are not infrequently themselves sources of irritation. When a bone is broken, for example, the pain which is induced by movement, and the diminished advantage at which the muscles connected with the bone act, are means whereby such irritant as is afforded by movement is diminished. So, too, in acute peritonitis we have a very well-marked example of this condition. The pain, or, at all events, the stimulation of afferent nerve-fibres in the peritoneum, is such that abdominal movements connected with respiration are completely inhibited; when pain is relieved by the administration of opium in large doses, though the peritonitis itself is unaltered, the abdominal respiratory movements reappear.

With regard to increased temperature, the matter is more difficult, though it is known that the growth of almost all pathogenetic micro-organisms is impaired by temperatures above about 37° C. We shall see when we come to discuss fever that one view of the process is that it is a natural endeavour on the part of the body to inhibit the growth of invading micro-organisms and to destroy the toxins which they produce.

III. **Conditions necessary for Repair.**—(i.) **Absence of Irritant Action and Inflammation.**—In considering repair, though no doubt the line is a hard one to draw, it must clearly be recognised that repair in any part essentially depends upon the action of a factor $x$, the intensity of which is insufficient to cause inflammation in that part. In other words, repair is the result of tissue stimulation and not of tissue irritation. That $x$ may be a stimulus in one case and an irritant in another case is clear: the pressure which, acting on skin, simply leads to proliferation of epidermis and the formation of a callosity, would, if acting on the cornea, lead to severe inflammation and necrosis. It follows from this that the effects produced by $x$ upon a *given* cell depends upon its intensity. It cannot act upon the same cell at the same time both as an irritant and as a stimulus, for the results of its action as an irritant are degenerative, while the results of its action as a stimulus are proliferative. The cell's growth may either be enhanced or it may be impaired, but both events cannot take place at the same time. We may therefore say that inflammatory changes must be absent from the seat of repair.

Nevertheless inflammation in one place must, at least theoretically, always be associated with repair at another. For the action of any irritant becomes gradually weaker the further one proceeds from the seat of application of the irritant, and hence it follows that at some point on the periphery the irritant merges into a stimulus, and the degenerative changes of inflammation merge into the proliferative changes of repair, always assuming that the tissues are capable of responding to the stimulus. So also, since an irritant which leads to inflammation must, during the retrogressive processes which constitute resolution, at some time or other be weakened to such an extent that it no longer acts as an irritant but as a stimulus, it follows that the subsidence of an inflammation must of necessity be accompanied by repair. As has already been said, resolution and repair go hand in hand.

The statement that inflammatory changes must be absent from the seat of repair requires a little closer examination. For nothing is commoner in any microscopical specimen of chronic inflammation than to find evidence of repair and of acute inflammation side by side. Thus, in a mass of cicatricial tissue which is filling up the space left in a lung after a focus of tubercular inflammation has broken down, agglomerations of leucocytes indicative of acute inflammation are frequently seen, so that almost in the same microscopic field one may have inflammation and repair side by side. But they are never present together at one and the same spot. Again, it is not uncommon to find that tissue which is on the way to repair has itself become inflamed, and in this case, reparative changes and inflammatory changes are apparently commingled. But that this is not really the case can usually be seen on careful examination of the proliferated cells, for in them degenerative changes are generally recognisable; in spite of the apparent coincidence, inflammation is the only process at work.

It is because such appearances as those described in the last paragraph are common, and because on the outskirts of an area of inflammation, proliferative changes of cells are evident almost at the moment when inflammation commences, that proliferative changes are regarded by some authors as a part of inflammation. Nevertheless any granulating wound shows that repair is most advanced where the irritant acts with least intensity, or, in other words, where the irritant becomes merged into a stimulus, that repair is less and less advanced as one proceeds towards the part where the irritant acts with greater and greater intensity, and that immediately beneath the free surface of the wound where the irritant is most intense, and where the inflammation, as evidenced by hæmorrhage, by exudation, by migration, is acutest, repair is completely absent. These facts, coupled with the fact that proliferation of cells in normal physiological life is a process quite independent of inflammation, seem to indicate that the cell proliferation which occurs after a part has been subjected to the action of an irritant, is of itself a separate process from the true inflammatory process.

From a histological point of view, the distinction is perhaps a small one, but therapeutically at all events, recognition of the fact that repair at any spot is dependent upon the cessation of irritation at that spot is of great importance.

(ii.) **Presence of a Stimulus.**—Now, though repair depends upon the cessation of irritation, it depends equally upon the maintenance of a stimulus to cell proliferation: when a stimulus is wanting, repair comes to a standstill. This condition may be seen in the case of an indolent ulcer, which for weeks or months may show no attempt at repair. The treatment for such an ulcer is the local application of some mild caustic, for the surgeon knows that such cell destruction to the superficial part of the sore as results from application of the caustic is more than counterbalanced by the cell proliferation which that caustic induces in parts at a distance from the surface. He procures inflammation, not because inflammation repairs the wound directly, for inflammation causes a greater wound at first, but because every inflammation as it subsides brings repair in its train.

(iii.) **Increased Nutriment.**—For the occurrence of repair, besides the existence of a stimulus to cell proliferation there is also the necessity for the supply of an increased amount of nutritive material. This indeed is but one of the laws of growth under all conditions. Since active hyperæmia and increased output of lymph are, under normal circumstances, the means whereby increased amount of nutriment is brought to tissues which are in need of such increased nutriment, we must assume that the inflammatory exudation is the chief, though perhaps not the only source of the nutriment which is supplied to the cells whose proliferation constitutes the first stage in repair. By some authors it is held that the fibrin network formed in the exudation, or even some of the migratory cells first appearing at the seat of inflammation (finely and coarsely granular oxyphil cells), also subserve the same purpose, and there is no doubt that the young connective tissue and endothelial cells of which reparative tissue is composed possess phagocytic powers. But, as in the case of all phagocytes, there is a doubt whether the function is nutritive or scavenging.

(iv.) **Capability of Cells for Division.**—For the occurrence of repair yet another factor must be present. It is essential that the cells upon which the stimulus acts shall be capable of division. This point is so obvious that it calls for no further remark, but the absence of repair in certain cases of inflammation depends apparently upon the absence of this factor.[1]

For the occurrence of repair, therefore, at any spot, four conditions must be satisfied :—

(i.) Irritant action, and therefore inflammation, must be absent from the spot.
(ii.) A stimulus to cell proliferation must be present.
(iii.) There must be a sufficient supply of nutrient material at hand.
(iv.) The cells upon which the stimulus acts must be capable of proliferation.

Now, if we imagine heat of 60° C. to be applied for three minutes to the healthy skin of any part over the area of a circle whose radius is 1 centimetre, we shall find that these four conditions obtain at a certain distance from the periphery of the focus of inflammation, and the same would be true if the radius of the circle had been 2 centimetres instead of 1 centimetre, excepting that the two peripheral regions of potential repair would not coincide. Moreover, if after heat has been applied over the area of a circle whose radius is 1 centimetre, and its results have become manifest, heat be applied over the area of a concentric circle whose radius is 2 centimetres, it is obvious that the zone of potential repair formed at first will become merged in the inflammatory region caused by the second application of heat. But there will still be found a zone of potential repair at the periphery of the larger circle. Repeated applications of heat in ever widening circles will always produce the same results—inclusion of what was earlier the reparative zone in what is now the inflammatory region, appearance of a fresh reparative zone in what was earlier normal skin—until no normal skin is longer available. These imaginary cases are types of the conditions that obtain when an irritant, organised or unorganised, acts locally. Leaving exceptional cases out of consideration for the present, we may say that around every inflammatory focus there is a zone in which the conditions necessary for repair are satisfied. It is quite immaterial whether the irritant is organised or unorganised, whether it spreads or is localised, whether it has acted for a longer or for a shorter time, whether its intensity is greater or less. These factors modify the extent of the inflammation, the extent of tissue-disorganisation, the size of the area over which repair will be necessary, the distance from the centre of the focus of irritant action at which the zone of potential repair shall be situated, and so on, but such a zone exists whatever the character of the irritant. In the same way the conversion of this zone of potential repair into a zone of actual repair is independent of every consideration save that it itself should not fall under the sway of an irritant.

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[1] *Cf.* Chapter XII.

Apart from the last-mentioned contingency, the condition of the tissue cells liable to proliferation in reparative zones is always the same, so that, whatever the pathological sequels may have been in parts other than the reparative zone, in this region the same changes always take place. Hence the essential phenomena of repair are everywhere identical. Inflammation may be followed by abscess-formation, by ulceration, by gangrene, or by none of these, but a zone of potential repair is formed in each case alike, and if the potential repair becomes definitive, the kind of tissue which is produced is the same whatever may have been the type of the inflammation that preceded it.

Two reservations, however, are necessary. Where the conditions of repair involve layers of epithelium in addition to deeper structures, or to their exclusion, the phenomena accompanying epithelial repair are superadded to the other changes or constitute the whole of repair, respectively. But with these exceptions the statement is true that repair tissue and the phenomena of repair under all conditions are essentially the same.

Now it has been said above that when the irritant does not cease to act the sequels of inflammation are pathological. But it is obviously possible that an irritant may cease to act *after* it has led to pathological sequels of inflammation, and therefore that the pathological sequels may themselves be followed by physiological sequels taking place in parts whose vitality has not been irreparably lowered by the persistence of irritant action. As a matter of fact this sequence of events is exceedingly common. Repair occurring under such conditions, however, is generally complicated in some degree by the pathological sequels taking place in the neighbourhood. For this reason repair following obvious pathological sequels of inflammation was long regarded as differing in kind from repair taking place in the absence of obvious pathological sequels. Though this is certainly not the case, it will be advisable to delay the detailed discussion of repair generally until the pathological sequels of inflammation have been considered.

IV. **The Pathological Sequels of Inflammation.**—Since the pathological sequels of inflammation are due to the persistence of irritant action, it follows that the factors which lead to these sequels are primarily the conditions which obtain in inflammation itself. In this part of the subject, therefore, we shall have to deal with excessive destruction of tissue elements, excessive exudation of fluid, excessive migration of wandering cells. Now the persistence of irritant action may depend either upon some peculiarity of the irritant itself or upon some peculiarity of the tissues upon which the irritant acts. As examples of the first condition may be given the pyogenetic bacteria generally. By their powers of multiplication in the tissues and of forming specific toxins, they have a greater natural tendency to cause persistence of inflammation than irritants such as aseptic incisions, the duration of whose irritant action is more or less limited. As an example of the second condition may be mentioned the different manner in which diabetic, alcoholic, or albuminuric patients react to a given irritant as compared with the manner in which a healthy person reacts to the same irritant. Thus pneumonia in a previously healthy person will probably end by simple resolution and recovery, whereas in a drunkard it is not unlikely to end fatally perhaps after the supervention of abscess or gangrene of the lung.

All the pathological sequels of inflammation are of a degenerative type, and in all of them death occurs whether of individual cells or of whole masses of tissue. This is only what might be expected, since they depend upon the persistence of irritant action, which of itself induces inflammatory degenerative changes. So also one can infer from the persistence of the irritant action that in the pathological sequels, degenerative changes play a far more prominent part than in cases of inflammation where irritant action does not persist. But there is no real line of demarcation between "inflammation" and the "pathological sequels of inflammation," just as there is no real line of demarcation between "action of an irritant" and "continued action of an irritant"; we shall therefore find that whatever may be the macroscopic peculiarities of the pathological sequels of inflammation, microscopically and essentially the pathological sequels are only exaggerations of the same processes that occur in the simplest inflammation. There is, consequently, the widest antagonism between the pathological and the physiological sequels of inflammation.

The conditions about to be described may be included under the two following headings: (A) Suppuration and abscess-formation; (B) Gangrene and necrosis in their various forms.

(A) **Suppuration and Abscess-Formation.**—Suppuration and abscess-formation essentially consist in the production, as the result of continued irritant action, of the fluid called "pus." It will be well first to describe the characters of pus and afterwards to discuss the conditions of its formation.

(i.) **The Characters of Pus.**—In its simplest form pus is a fluid, creamy both in colour and in consistency, with a mean specific gravity of 1030–1033, an alkaline, but, according to Ewald, not infrequently an acid reaction, and a faint mawkish odour. In the vast majority of cases it does not coagulate spontaneously, but if allowed to stand it separates into two layers. The upper of these is known as "liquor puris"; it is a transparent, colourless or straw-coloured fluid, and resembles blood-serum. The lower layer is opaque and holds the suspended solid elements of the pus. Liquor puris chemically is an albuminous fluid closely similar, so far as its saline constituents are concerned, to blood-serum and lymph. It contains 6·7 per cent. of proteid, or slightly less proteid than blood-serum, but it contains a larger amount of cholesterin. Nitrogenous extractives, such as leucin and tyrosin, and albumoses are also found in liquor puris. It is perhaps owing to the presence of albumoses in pus, and to the power possessed by many of these substances of inhibiting coagulation that the absence of auto-coagulability of pus is due. As we shall see, however, this is not the only possible explanation of the fact. A large quantity of mucus is also present, and the "ropiness" which this substance shows on addition of caustic potash is used as one of the tests for pus. So far as the above characteristics are concerned, there is but little difference whether the pus has been derived from an "acute" or from a "cold" abscess, but with regard to the deposit from pus, the difference in the two cases is marked.

If the pus come from an acute abscess, the deposit consists of colourless round cells whose outline is well defined, whose protoplasm is generally granular, and whose nucleus is generally either multipartite or multiple. If the cells be examined on the warm stage, it will commonly be found that a large number of them show amœboid movements. The granules in the cell protoplasm are not stained by osmic acid and are dissolved very readily by acetic acid; they are therefore not fat, a matter of some importance in view of the fact that pus-cells are very liable to undergo fatty change.

If the pus come from a cold or chronic abscess the deposit often does not show the presence of a single cell, but, on the contrary, consists of granular amorphous *débris*. Some of the larger masses of *débris* show signs of fatty change and the liquor puris may contain free fat globules. These points, taken in conjunction with the fact that in less completely disintegrated pus, pus-cells are frequently found containing definite fat droplets, suggests that the *débris* really consists of broken down and fattily degenerated pus-corpuscles. It is well in accordance with this view that an amorphous deposit from pus is associated with chronicity of the abscess.

Taking pus as described above we find that it may show many differences and may undergo many changes. Instead of being "creamy" and having a specific gravity of 1032 it may be "watery" and have a specific gravity of, perhaps, 1020; under these conditions cells are scantily present. Or it may be mixed with blood so that its colour may vary from pink to bright red or from pale brown to a deep chocolate. When an abscess contains much blood, the blood may be present in altered coagula so that the pus has a grumous appearance, or it may be evenly distributed throughout the fluid. According to these differences in macroscopic appearances the microscopic characters of the pus will differ also; in one case apparently normal red blood-corpuscles may be present, in another only granules of blood-pigment and disintegrated fibrin. Under certain circumstances pus may be distinctly green in colour.

The odour of pus also varies. Though commonly it has a mawkish smell only, when it is associated with disease of the middle ear, as in many cerebral abscesses, it is generally fœtid and often so to an extreme degree. Collections of pus yielding this fœtor have undergone putrefactive changes. Collections of pus in the neighbourhood of the intestinal tract, even when they have no obvious connection with the bowel, almost invariably have a fœcal odour. In some cases putrefactive changes in pus are associated with the evolution of considerable quantities of gas.

*Sources of Liquor Puris and Pus-corpuscles.*—When we consider that suppuration is one of the results of persistent irritant action, that the liquor puris is practically identical with blood-plasma in its composition and characters, that pus-cells are amœboid, granular, and multinuclear colourless cells, and that in inflammation exudation of fluid occurs along with migration of leucocytes, particularly of the finely granular oxyphil type, it is almost impossible to resist the conclusion that liquor puris is liquor sanguinis, though no doubt somewhat altered in composition, and that pus-corpuscles are migrated leucocytes. Irresistible as this conclusion seems, when it was first put forward by Cohnheim it met with violent opposition, notably at the hands of Stricker. It would not be profitable after these years to enter into the details of the controversy, but the view maintained by

Stricker was that, as the result of irritant action, tissue elements of all kinds revert to their embryological condition. He therefore regarded pus-corpuscles as being modified tissue-cells. At the present time it is generally held that the greater number of pus-cells are derived from the blood; but there is growing up a tendency to look upon some pus-cells as direct derivatives of wandering cells found in connective tissue, and if this view be correct, Stricker's contention must to some, though to a greatly modified extent, be accepted. Until recently Cohnheim's view, that all pus-cells are derived from the blood, was alone received by almost all authorities.

The view that pus-corpuscles are in the main hæmal wandering cells derives support from examination of pus stained after the methods originated by Ehrlich in his work upon leucocytes. The greater number of pus-cells in an acute abscess are leucocytes of the finely granular oxyphil (neutrophil, polynuclear) type, but coarsely granular oxyphil (eosinophil) cells, and hyaline cells of different sizes (the mononuclear cells of Continental writers) are also to be found, the latter not infrequently in considerable numbers. The proportion of finely granular oxyphil cells is greater and of hyaline cells is less the earlier in the suppurative process the pus is examined; the exact converse is also true. These statements, however, are only general, as there is the greatest diversity in the nature of the cells present in pus.

With regard to the origin of cells in pus other than oxyphil cells (that is to say, the cells which have been grouped together above as "hyaline") our information is very meagre. It is quite unknown whether they are of blood or of tissue origin, though the latter is most probably the case; if derived from tissues, whether they are derived from connective tissue corpuscles or from endothelial cells; whether they correspond, as their microscopical characters in most cases would suggest, with the cells known as lymphocytes; whether they are pre-existing cells or are descendants of pre-existing cells that have proliferated owing to stimulant action of the irritant; or indeed whether they own a single origin at all. Practically all that is known concerning them is that they are phagocytic (a fact against the idea that they are lymphocytes) and that they usually appear on the scene later than the granular oxyphil cells.

The irregular forms shown by the nuclei of the finely granular cells in pus probably depend upon fixation of the cells while they were still in active amœboid movement, for the nucleus of an amœboid cell to some degree participates in the alterations in shape of the cell itself. Multiplicity of nuclei in a pus-cell is to be regarded as a sign of degeneration or disintegration of the nucleus and not of proliferation. That considerable amœboid movement may be associated with commencing degeneration of cells is also shown by the movements which take place in red blood-corpuscles when they are about to undergo Maragliano's degeneration (*cf.* p. 147). The nucleus of hyaline cells in pus is commonly circular or oval and these nuclei stain far more feebly than do the nuclei of the granular oxyphil cells.[1]

(ii.) **Abscess.** — When collections of pus occur in the middle of organs or of complex tissues, or when they are localised in some definite portion of a natural cavity in the body, they are generally known as abscesses, but when they are more or less free in pre-existing cavities, they sometimes receive special names. Thus, a collection of pus in the pleural cavity is known as an "empyema," in the pericardial cavity as a "pyopericardium," in a Fallopian tube as a "pyosalpinx," in a dilated pelvis of the kidney as a "pyonephrosis," in the anterior chamber of the eye as "hypopyon." Whitlows, boils, furuncles, and carbuncles are names for varieties of suppurative inflammation affecting the subcutaneous connective tissues or structures lying in them. Even clinically they are closely allied to abscesses; pathologically their mode of formation is identical. For their characteristics special works on surgery must be consulted.

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[1] Janowski believes that every suppuration begins by a collection of mononuclear cells at the stimulated spot. These become converted into polynuclear cells partly in the tissues where they are most powerfully stimulated, partly in pus itself; consequently in every fresh pus there is a certain number of mononuclear cells, but the number decreases with the age of the pus until at last none are left, while at the same time the number of polynuclear cells increases. With increase of cell nuclei there is also a new formation of (generally) fine or (rarely) coarse eosinophil granules. Later the granulation disappears and the cells and nuclei degenerate.

Pus-formation, however, need not lead to the collection of pus into an abscess; the pus may be discharged as quickly as it is formed. Examples of this condition are seen in ordinary superficial suppurating wounds and ulcers, and in gonorrhœa and dysentery.

When an abscess is being formed at any spot the pus which it contains is pent up under a greater or less degree of pressure, which of course causes the surrounding tissues to yield most where their resistance is the least. An abscess, therefore, tends to "point" in some one direction, and the pointing is in the direction of least resistance. This law explains the fact that an abscess invading the psoas muscle commonly points somewhere in the thigh, as well as the fact that a subcutaneous abscess bursts through the skin.

(*a*) *Mode of Formation.*—The mode of abscess-formation may best be studied by considering the changes that occur when a septic embolus is carried to an organ such as the liver, and there forms an abscess. At some point where the calibre of the blood-vessel is sufficiently small, the embolus which is circulating in the blood-stream becomes lodged and commences to exert its irritant action. As a result of this irritant action, inflammation is set up in the wall of the vessel; the vasa vasorum dilate and become congested, the circulation through them becomes more rapid, then it slackens and ultimately is arrested, but previous to stasis, exudation of fluid and migration of leucocytes have occurred. At the same time the irritant (bacterial toxin) causes degenerative changes in the tissue-cells (commencing with the endothelium of the blood-vessel in which the embolus lies), and many of the tissue-cells die. Thrombosis also occurs on either side of the embolus, and the direct effect of the irritant is intensified by the insufficiency of nutriment which the tissue receives. The leucocytes that have wandered from the blood-vessels and others that have come from the tissues collect at the seat of irritation, attracted thither we may suppose by positive chemiotaxis. There is thus formed around the embolus a mass of material consisting of blood-clot and of the disorganised elements of the vessel wall infiltrated with an albuminous fluid. In this mass are also numbers of leucocytes, of which some are living, but the majority of which have succumbed to the action of the toxin. This dead and disorganising tissue itself forms an irritant to surrounding tissues, but its importance as a direct irritant is small compared with its importance in serving as material in which growth of the septic bacteria, originally present only in the embolus, can take place. Finding a plentiful supply of nutriment and a suitable temperature, the bacteria multiply and their sphere of influence extends in all directions, with the result that the inflammation induced by the bacteria and their toxin also extends in all directions. In this way there is formed a mass of material surrounding the original embolus which consists of dead liver substance, dead vessel wall, blood-clot, etc., in which the only living elements are the bacteria and such leucocytes as have not succumbed to the action of the toxin. This mass is œdematous from the inflammatory exudation that has been poured out, but very commonly is denser than normal from the presence of fibrin formed in the exudation fluid and the number of leucocytes that has collected at the spot.

Before this condition has lasted very long, while, indeed, the preceding changes are going on, liquefaction of the doughy mass commences. Liquefaction is first recognisable in the very centre of the mass; probably in the case of a septic embolus, it begins in the embolus itself. As the inflammatory infiltration spreads, the extent of the liquefaction increases, so that in a fully formed abscess we have a central fluid mass—the pus—around which are arranged zones of solid material, gradually shading from a layer which is immediately about to break down into pus, and which therefore forms the wall of the abscess, through a zone of inflammatory tissue and a zone in which the proliferative changes of potential repair are taking place, to the normal substance of the liver.

The fluid portion of pus is to a very large extent inflammatory exudation fluid, but the liquefaction of solid material which takes place in the centre of a purulent focus shows that the exudation will not wholly explain pus-formation. There must be an actual solution of certain solid substances, in particular the altered tissue elements of the part must be dissolved. So far as we know, this change can only be brought about by a process of digestion, and for it a proteolytic ferment is necessary. Some of the chief pyogenetic micro-organisms, and notably *Staphylococcus pyogenes aureus*, form a proteolytic ferment as one of the products of their life-history, and it is not difficult to suppose that in ordinary abscess-formation, which is most commonly associated with this micro-organism, liquefaction is carried out by a process of proteolysis initiated by the bacteria. This is the more probable as albumoses similar to those found in ordinary proteolytic digestion, and such nitrogenous extractives as leucin and tyrosin, are found in pus.

But *Streptococcus pyogenes* and several other micro-organisms which are definitely pyogenetic, form no proteolytic ferment, and it therefore becomes necessary in these cases to search for another explanation of the liquefaction that undoubtedly occurs when these micro-organisms cause an abscess. This explanation is probably found in the properties of phagocytic cells. It has already been pointed out that such cells attack solid substances, and bring about their solution both by extra-cellular and by intra-cellular digestion; the numbers of phagocytes present in tissue which is about to break down into pus is so great, and the degenerated condition of the tissue elements themselves is so marked, that the occurrence of solution by phagocytic action seems highly probable. We know that phagocytes can dissolve cat-gut; it is not difficult to suppose that they can bring about the solution of degenerated inflammatory tissue. Nor is the fact that very large numbers of phagocytes in pus are dead an insuperable difficulty, for not only are very many of the leucocytes present still living, as shown by their amœboid movements, but also living cells are not necessary to the occurrence of digestion. Of this fact the commercial preparation of dried pepsin from the gastric mucous membrane of the pig is sufficient evidence.

(*b*) *The Part played by the Irritant.*—The part played by the irritant in abscess-formation is a very important one. An abscess is essentially a liquefied inflammatory focus in which the number of wandering cells is so great that their presence forms the dominating feature of the inflammatory products. Now since the attraction of wandering cells to a given point—positive chemiotaxis—and the absence of attraction or possibly actual repulsion—negative chemiotaxis—depend upon the concentration of the chemical substance as well as upon its nature, it is intelligible that the result of persistent irritant action will in some cases be the formation of an abscess and in other cases not.

1. *Intensity of Irritant.*—If the irritant be very slight, as when but few micro-organisms and those of a very low order of virulence are introduced into the tissues, it is possible that it may induce very feeble positive chemiotaxis; it is possible, too, that it may be dealt with by such cells as are present at the spot, and it is highly probable that it may be destroyed *in situ* by the fluids of the tissues in which it lies. Under any of these conditions, the number of wandering cells at the spot is very small, even though from the inflammation which is present they may be more numerous than normal. And in any case the amount of exudation and the numbers of wandering cells present is insufficient of itself to constitute pus, while liquefaction of dead tissues does not take place and aid the process, principally because the irritant is of so low an order that hardly any dead tissue is produced which can undergo liquefaction. It must be remembered that "pus" is a clinical term, and though, of course, in the above example, pathologically, the process is identical, excepting in degree, with the process obtaining in the formation of a large abscess, it is convenient to say that in the one case pus is formed, in the other case it is not formed.

A condition of this kind probably obtains in all "aseptic surgery." We can hardly imagine that a surgical operation, even when carried out with the greatest care, is absolutely aseptic in a bacteriological sense—the impossibility of sterilising the skin in any case precludes this; but we must assume, since the inflammation is minimal, that irritation has been minimal, and that though some micro-organisms have gained access to the wound during the operation, they have been so few and of such a kind that the body has destroyed them before they have been able to multiply and form any important amount of toxin.

At the other extreme we also find cases in which pus is not formed. If the irritant be very intense, or, particularising, if being a micro-organism it forms a toxin of very great intensity, either paralysis of wandering cells or negative chemiotaxis occurs, with the result that hardly a wandering cell is found at the seat of irritation. In these cases the intensity of the irritant may be sufficient to cause so rapidly spreading a destruction of tissue, that sufficient time is hardly given for the development of inflammation, or the disorganised tissue may become softened by infiltration with exuded inflammatory fluid in which no leucocytes are found. These conditions are not very infrequently found in internal organs, when septic emboli of exceptional virulence have lodged within the blood-vessels. Microscopically complete disorganisation of the tissue may be recognisable, and yet no pus is formed. In the condition known as acute yellow atrophy a large portion of the liver may be in such a softened condition as this.

A condition lying between the above and definite pus-formation occurs in septic cellulitis, where inflammation spreads very rapidly in the cellular subcutaneous tissue of perhaps a whole limb in a few hours. The copious inflammatory exudation fluid in these cases contains wandering cells, it is true, and in considerable numbers, but the fluid is sero-purulent and is not pus. In very severe inflammations of this description, the irritant may have produced changes in the vessel walls, so severe, that actual hæmorrhage takes place, and the exudation is not only sero-purulent but is also blood-stained.

The intensity of the irritant is therefore of great importance in determining pus-formation. It must neither be too great nor too small, for under either of these conditions pus is not formed. After what has already been said, it is unnecessary to repeat that the nature and the vitality of the tissue upon which the irritant acts must be considered along with the intensity of the irritant itself in this connection.

2. *Nature of Irritant—Pyogenetic Micro-organisms.*—We must now consider the nature of the irritant in connection with pus-formation.

After Ogston of Aberdeen had in 1881 made known the fact, that in every one of the large number of acute abscesses which he examined he found the presence of micro-organisms, and after this statement had been confirmed by several other observers, it was for a short time held that pus-formation is essentially a result of microbial action, and that where no micro-organisms are present, there no pus is formed. But this view was not universally accepted. It was found by several investigators, if silver nitrate, mercury, turpentine, ammonia, mixtures of croton and olive oils, and many other substances be placed under the skin with antiseptic precautions, that a fluid indistinguishable from pus is produced. For some time these experiments were inconclusive, because of the difficulty in procuring complete asepsis. Moreover, supporters of the view that bacteria are essential to pus-formation were strengthened in their contention, that in cases of so-called sterile pus, asepsis was not complete, by the undoubted fact that the more stringent the precautions taken, the less common is it for pus to be produced. But when Councilman and Wyssokowitch and Buchner made known the results of their several experiments, it was allowed that the presence of living micro-organisms is not essential to pus-formation, however commonly the two conditions may co-exist. Councilman introduced, with strict antiseptic precautions, sterile glass capsules containing a sterilised mixture of croton and olive oils under the skin of animals and allowed the wounds to heal completely. When healing was complete, he broke the capsules subcutaneously by a smart blow on the surface, and thus the irritant came to act upon the tissues under conditions in which apparently no suspicion of microbial contamination could be entertained.[1] Wyssokowitch and Buchner worked with sterilised cultures of micro-organisms, amongst which were *B. anthracis*, *Streptococcus pyogenes*, *Staphylococcus pyogenes aureus*, *B. prodigiosus*, *B. subtilis*, and many others: in spite of the fact that in all cases the micro-organisms inoculated were dead, with all of them a sterile pus was produced.

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[1] When we come to consider latency of bacteria we shall see that micro-organisms may apparently remain quiescent in the tissues until some condition of lowered resistance on the part of their host renders their multiplication possible. Councilman's experiments are not quite conclusive, therefore, as it is

In this position the question is at the present day, and we may say that pus-formation is not indissolubly bound up with the presence of bacteria, for many chemical substances, if inoculated under strict aseptic conditions into living tissues, may produce a pus which is completely sterile. Nevertheless in the vast majority of cases pus-formation and the presence of bacteria are linked together. However, even if bacteria be present, it is not necessary that they should be living, for Buchner showed that pus-formation is more closely bound up with the bodies of bacteria than with the toxins which those bacteria produce when living (extra-cellular poisons). For he found that when a cultivation in broth is filtered, the sterile filtrate which contains the extra-cellular poison does not lead to abscess-formation when injected subcutaneously with strict antiseptic precautions, whereas the bodies of the bacteria, after repeated washing has freed them from all traces of the filtrate, and after they have been killed, lead invariably to the formation of sterile abscesses when injected subcutaneously in sufficient quantities. Whether the abscess-formation in the latter case is due to the action of the intra-cellular poison or to the physical properties of the bacteria, or to both of these, it is impossible to say at present. Whichever explanation be the true one, it is nevertheless certain that when bacteria are living and multiplying, the chances of pus-formation are increased. A number of

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possible that micro-organisms might have gained access to the depth of the wound when introducing the glass capsules, and have remained latent, until the injury produced by the blow necessary for fracture of the capsule and the irritation produced by the fragments of glass and by the mixture of oils had lowered the vitality of the tissues to such an extent that they could no longer resist growth of the bacteria. The fact, too, that no cultivations can be obtained from any pus produced in this way does not necessarily prove that bacteria had no part in the pus-formation ; at most it proves that no *living* bacteria were present of such a kind as normally grow on the usual laboratory media. This is but another example of the difficulty of obtaining absolute proof in scientific investigations.

dead bacteria sufficient to produce macroscopic suppuration can hardly be introduced into the tissues, except experimentally; for the production of suppuration by living bacteria, the initial number introduced may be very small, and thus an accidental entrance may be easily effected.

One of the objections raised to the above experiments by supporters of the view that pus is never formed in the absence of micro-organisms, was that the fluid produced in such experiments as those of Councilman and Buchner, though somewhat like pus, is not absolutely like pus. They therefore maintained that in these experiments pus, as the surgeon understands the term, is not produced. It must be granted that in most cases this objection is reasonable, if by pus is meant such a fluid as is obtained from an acute abscess; but when one bears in mind that in cold abscesses the fluid is frequently curdy, that instead of cells one generally finds only a granular and amorphous *débris*, and that in spite of these differences the surgeon still speaks of the fluid as "pus," the objection cannot be allowed. According to Janowski the morphology of pus is the same whether it is caused by micro-organisms or by sterile chemical irritants, such as mercury. He found that not only are the same kinds of cell present in both cases, but that the stages in the pus-formation follow one another in the same order (though more rapidly when the pus is caused by chemical irritants). In all cases, therefore, septic and aseptic, the fundamental processes are the same, and whether the irritant be organised or unorganised, assuming that the intensity of the irritant and the reaction of the tissues are suitable, persistence of irritant action may lead to pus-formation. It is, however, probable that where the irritant is particulate, the liability to pus-formation is greater than under the opposite conditions; this, no doubt, is because in the former case persistence of irritant action at a given spot is more readily attained.

Under suitable conditions the presence of any species of micro-organism may *theoretically* be associated with pus-formation, and examples of pus-formation in connection with bacteria which do not usually lead to suppuration are by no means rare.

Thus *B. diphtheriæ* and *V. choleræ asiaticæ*, when introduced subcutaneously into animals whose resistance to these micro-organisms is very considerable, readily cause the formation of localised abscesses. In man, *B. typhosus* and *M. pneumoniæ* are known to lead to pus-formation, the latter micro-organism being very commonly found in purulent otitis media and in empyema, and the former having been found in pure cultivation in the abscesses which sometimes occur in the later stages of typhoid fever.

But though any species of micro-organism may theoretically be associated with pus-formation, and though some species, generally not associated with suppuration, on rare occasions have actually been known to cause suppuration, certain of the micrococci are so frequently found along with pus that they are termed "pyogenetic cocci." Of these the commonest are *Staphylococcus pyogenes aureus* and *albus*, *Streptococcus pyogenes*, *Micrococcus gonorrhœæ*, and *Micrococcus pneumoniæ*. Besides micrococci certain bacilli and moulds are also associated with pus-formation. Such are *B. tuberculosis*, especially when it affects bones and joints,[1] *B. anthracis*, which causes "malignant pustule" in man, *B. pyocyaneus*, which from the formation of a soluble pigment (pyocyanin) causes pus in which this micro-organism is present to take on a bluish-green colour, and *Actinomyces*.

(*c*) *Modes of Spread of Pyogenetic Micro-organisms.*—When describing the process of abscess-formation, it was said that an abscess increases in size by disintegration into pus of that portion of the abscess wall which is immediately in contact with the pus that is already formed. Besides this mode of extension by continuity of tissue, the suppurative effects of an irritant may spread in two other ways: (1) by the lymphatics, (2) by the blood-stream.

1. *By the Lymphatics.*—When an irritant spreads by the lymphatics its action may become marked at a considerable distance from the point of entry of the irritant. Thus, an abscess

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[1] The suppuration which occurs when *B. tuberculosis* affects the lungs is due rather to the pyogenetic cocci which gain access to the tubercular foci than to the tubercle bacilli themselves; the condition is one of "mixed infection."

in the inguinal region may depend upon a septic abrasion on the heel or on the external genitals, an abscess in the axilla may depend upon a septic wound on the hand. When such an abscess occurs it is situated in the corresponding lymphatic glands, at any rate at first, and the reason why the irritant produces an abscess here, instead of at its point of entry, is because the lymph-flow from the inflamed abrasion carries the irritant along with it to the nearest lymphatic gland before time has been given for the formation of an abscess around the original point at which the micro-organism entered. Once lodged in the gland, however, the conditions are such that multiplication *in situ* of the bacterial irritant is possible, and hence it produces an inflammation which ends in suppuration. A small amount of pus, however, is generally formed at the seat of abrasion also. Negative chemiotaxis or feeble positive chemiotaxis at the seat of entry of the micro-organism probably also plays a part; whether because of the virulence of the micro-organism, or because of the feeble resisting power of the individual, the bacteria are not destroyed locally, but in a living and active condition travel by the lymphatics to a gland.

Under ordinary circumstances the lymphatic vessels of the part show no signs of implication in the process—they are simply paths whereby the irritant travels; but sometimes, and especially if the irritant is of high intensity, inflammation occurs in the walls of the lymphatic vessels and in their immediate neighbourhood, giving rise to the appearance of those fine red, and perhaps painful, lines on the surface of the limb which mark the course of the inflamed superficial lymphatics and are characteristic of lymphangeitis. On the other hand, lymphangeitis may occur without obvious implication of the lymphatic glands.

2. *By the Blood-Stream.—Pyæmia, Septicæmia, and Sapræmia; Ulcerative Endocarditis.*—When an irritant, such as *Staphylococcus pyogenes aureus* or *Streptococcus pyogenes*, gains access to the blood-stream, its effects vary according to circumstances. In some cases it probably is followed by no ill effects, for experiment shows that the blood is capable of destroying considerable numbers of bacteria when they are injected into the

veins of healthy animals; but with such cases we are not concerned at present. If, however, the micrococcus be of the right degree of virulence to lead to pus-formation, and if it become lodged anywhere as a septic embolus, it probably always causes a local abscess. If, on the other hand, it be of so great a degree of virulence that it leads to negative chemiotaxis, abscess-formation is out of the question.

Now the two last-mentioned conditions correspond in some degree with clinical conditions in which micro-organisms have gained access to the blood-stream, and which are known as pyæmia and septicæmia. Along with pyæmia and septicæmia, it is convenient to consider an allied condition known as sapræmia. Popularly these three states are confounded under the one name of "blood-poisoning."

Pyæmia, septicæmia, and sapræmia have many points in common so far as the clinical symptoms met with in these conditions are concerned, but there are certain fundamental differences between the pathological processes in the three cases. Sapræmia—also called septic intoxication—is the simplest and will be described first. It agrees with septicæmia and pyæmia in that it depends upon the growth of micro-organisms and the formation of poisonous substances by them; it also, like they, depends upon the action of those toxic substances on the body. But sapræmia differs from pyæmia and septicæmia in that the micro-organisms are incapable of life within the blood and tissues, whereas in pyæmia and septicæmia the micro-organisms not only are capable of life within the blood and tissues, but actually gain access to them, are carried in a living condition to distant parts and produce toxic substances within the body itself. Though we must allow that both in pyæmia and in septicæmia the symptoms of the disease are due rather to the toxic substances formed by the micro-organisms than to the actual presence of the micro-organisms as such in the blood or tissues, there are the fundamental differences between sapræmia on the one hand, and pyæmia and septicæmia on the other hand, that in sapræmia the laboratory for the preparation of toxin is physiologically outside the body and the micro-organisms concerned are putrefactive and not pathogenetic micro-organisms, while in pyæmia and septicæmia the laboratory for preparation of the toxin is in great part physiologically within the body and the micro-organisms concerned are pathogenetic.

Now since in sapræmia the micro-organisms are putrefactive and incapable of existence in living tissues, it follows that for the occurrence of sapræmia not only must such micro-organisms be present, but also dead material capable of undergoing putrefaction must be present also. Moreover, since the symptoms of the disease are caused by the chemical products which these micro-organisms form in the dead material, it follows that those products must be in close connection with a large absorbing area of the living body itself. Such conditions as these are fulfilled when putrefaction occurs in portions of placenta left in the uterus after parturition, or in inflammatory exudation that has collected in the peritoneal cavity after abdominal operation, or in the fluid contained in deep abscesses or cysts. In these and all similar cases there is a cavity—physiologically outside the body—which holds a putrescible material, and if putrefactive micro-organisms gain access to this material, the chemical products of putrefaction are absorbed from the cavity by the body and produce the clinical symptoms of sapræmia.

Further, since the symptoms of sapræmia are due to the absorption of a chemical poison, the severity of those symptoms, speaking generally, will be proportionate to the amount of poison absorbed, and therefore to the extent of the absorbing area and the amount of material undergoing putrefaction. And since the chemical poisons in the blood are constantly being eliminated by excretory glands, in particular by the kidney, it follows that if the putrefying material is removed, absorption must cease, and the symptoms must disappear. In these points we have other important differences distinguishing sapræmia from septicæmia and pyæmia.

That this is the true explanation of sapræmia was experimentally shown long ago by Panum, who produced the condition in animals by injecting into them putrid solutions which he had previously boiled, and thereby had freed from all living elements. He also produced the same condition by injecting a solid substance which he separated from putrid solutions by precipitation with alcohol.

The actual condition of sapræmia being due to the presence in the blood of chemical substances unaccompanied by living micro-organisms, it follows that if blood taken from an individual suffering with sapræmia were injected into a healthy individual the effect produced in him—apart from accidents—would depend upon the amount of toxin introduced with the injected blood. Since the toxin thus introduced would be spread over the whole body of the second individual, and would be rapidly excreted by him, the experiment (unless the amount of toxic blood injected were enormous or the recipient particularly susceptible) would be followed by no ill effects of any kind; in particular, the second individual would not become affected with sapræmia. But if the disease of the first patient were not sapræmia, but septicæmia or pyæmia, the case would be quite different. For it has been already stated that in these two conditions micro-organisms gain access to the blood, and are capable of existence in it and the living tissues. If, then, blood from an individual suffering from pyæmia or septicæmia were injected into a healthy individual, not only would chemical substances of bacterial origin be injected, but also with them would perhaps be injected micro-organisms which (leaving questions of immunity out of consideration) would be capable of existence in the second individual. In this second individual the micro-organisms would multiply, form toxin and reproduce the pyæmic or septicæmic condition. Pyæmia and septicæmia are infective diseases, sapræmia is not infective.

We may now consider the differences between pyæmia and septicæmia.

The first point of difference between these two conditions that must be noticed is that in pyæmia secondary abscesses are formed, in septicæmia no abscesses are formed. In both conditions the same species of micro-organism may be concerned, in both it must have gained access to the blood-stream and must be capable of living in the blood-stream, in both it must multiply in the blood-vessels and form toxin; but from a clinical point of view, at least, this difference with regard to abscess-formation is fundamental.

Now the fact that in pyæmia secondary—or, as they are also called, metastatic—abscesses are formed, suggests that the action of the micro-organism is localised to certain points, and commonly it is only at the seat of these abscesses that the micro-organisms can be found; they are not found in the blood generally, or if present they are only present in very scanty numbers. The abscesses are very often secondary to some purulent focus elsewhere in the body, especially when that focus is closely connected with the venous system. Of all conditions liable to be the starting point of pyæmia a septic venous thrombosis is the most common. Thus pyæmia may occur after parturition when the clots in the uterine sinuses are invaded by pyogenetic micro-organisms from the uterine surface. So also septic thrombosis of a lateral sinus secondary to ear disease is very often followed by the formation of pyæmic abscesses in other parts. In either case, as the result of the growth of the micro-organisms and the softening of the clot, portions of the clot with the attached micro-organisms are broken off, carried away in the blood-stream and lodged in various parts, of which the lungs are the most common. Suppurative conditions of the medulla of long bones —septic osteomyelitis—is also a common starting point for the formation of pyæmic abscesses elsewhere.

In pyæmia the micro-organisms concerned are always pyogenetic. In the vast majority of cases they belong to the group of "pyogenetic cocci," and of these *Staphylococcus pyogenes aureus* and *Streptococcus pyogenes* are most commonly present. In septicæmia, on the other hand, the micro-organisms must be pathogenetic, but they need not be pyogenetic, though if we restrict the term "septicæmia" to those cases which clinically are known as such, the pyogenetic micro-organisms, and especially a diplococcus which on artificial cultivation shows itself to be *Streptococcus pyogenes*, are the organisms by far the most commonly found. From a pathological point of view, however, septicæmia[1] is a broader term and is used to cover all cases in which the micro-organism, whatever its nature, gains access to the blood and can be obtained from it. Thus in animals such as the guinea-pig and the rabbit, anthrax is a septicæmic disease, for the blood-vessels throughout the body are crowded with anthrax bacilli. Even with infective diseases which are strictly localised under usual circumstances, such as erysipelas when inoculated experimentally in the rabbit's ear, it is found in most cases that a short time before death septicæmia results and the streptococci are to be obtained from the heart's blood. And there is reason to believe that in quite a large number of local infective diseases in which death ensues some little time after inoculation, or in which the resisting powers of the individual are very small, the last stage of the disease consists in the production of a general blood infection.

We are not well acquainted with the conditions in man with reference to this point, but at least in diphtheria it is certain that in rare cases diphtheria bacilli gain access to the blood, and after death are to be obtained from the spleen, heart's blood, etc., however strictly the bacilli may have been localised in the superficial tissues during the earlier portion of the disease. So also erysipelas in man sometimes terminates in a general pyæmia, and cases of generalised vaccinia, with production of scattered vaccinia vesicles over the body, have been recorded, though they are not common. In influenza, too, the disease is probably localised for a short time in the tissues before it invades the blood secondarily and produces a condition which in pathological language is a septicæmia, but which, clinically, would not be recognised as such.

The whole of this part of the subject, however, is intimately bound up with questions of immunity and must be left for the present in the above position.

Both in pyæmia and in septicæmia the extent of the initial lesion by which the micro-organisms concerned effect their entrance into the body is of comparatively little importance;

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[1] No doubt in course of time the word "Septicæmia" will give place to another and more suitable term.

a mere scratch is sufficient to allow of the development of a fatal septicæmia if the micro-organisms are of excessive virulence. For some reason with which we are as yet imperfectly acquainted, micro-organisms which have multiplied in the peritoneal cavity are of such exceptional virulence, and it is for this reason that wounds incurred by pathologists while performing autopsies are far more liable to be followed by septicæmia when the case has been one of septic peritonitis than when the patient has died of any other disease.

*Ulcerative Endocarditis.*—In the cases of pyæmia hitherto considered a primary focus of suppuration is recognisable, but not infrequently multiple abscesses appear in different parts of the body without the existence of any obvious suppurative lesion. In these cases cardiac symptoms and murmurs are often present, and after death an ulcerative condition of the cardiac valves is found. The cardiac lesion is here the immediately antecedent cause of the pyæmic abscesses, for in the vegetations on the valves pyogenetic micro-organisms are constantly present; *Staphylococcus pyogenes aureus* and *albus*, *Streptococcus pyogenes*, *Micrococcus pneumoniæ*, and *Micrococcus gonorrhœæ* have all been found in the vegetations. Where this is the case, association of the secondary abscess with embolism of particles of the septic vegetations on the valves is easy, especially in view of the fact that in these cases the metastatic abscesses are most commonly found in the spleen and kidney, regions in which simple embolism and infarction are especially common in valvular disease of the ordinary kind.

But the exact meaning of the valvular condition itself is not so easy to determine. Probably in the majority of cases the ulcerative condition is superposed upon an old simple chronic valve lesion. But for this to occur it is necessary that the micro-organisms present in the vegetations should previously have gained access to the blood. In some cases, as for example when the valvular lesion is associated with the presence of gonococci in the vegetations, we may regard the ulcerative endocarditis as a direct result of infection of the blood at the seat of local gonorrhœal suppuration in the urethra or vagina, and the metastatic abscesses in the organs as direct effects of embolism from the cardiac valves. In that case the urethral suppuration is primary, the ulcerative endocarditis is secondary, the metastatic abscesses are tertiary. In other cases the cardiac condition is itself a tertiary manifestation, for in ulcerative endocarditis the valves on the left side of the heart are always involved to a greater extent than those on the right side, and unless the valves on the left side have been directly infected by emboli sufficiently small to pass through the pulmonary capillaries, it is necessary that a secondary focus of suppuration should be formed in the lungs from which the left valves of the heart may be tertiarily affected. As a matter of fact, where the starting point of a pyæmia is a septic venous thrombosis, secondary abscesses in the lungs are common, and hence tertiary affection of the left cardiac valves may readily be explained. Nevertheless it is also conceivable that groups of two or three living cocci may become detached from the primary focus and circulate independently, passing through the pulmonary capillaries and becoming ultimately attached to the valvular endocardium at the lines where the segments of the valves come into contact during cardiac systole. In this way the occurrence of ulcerative endocarditis as a secondary manifestation would be rendered possible.

There exists, however, a not inconsiderable number of cases in which the ulcerative endocarditis is apparently primary. That it is so in reality our knowledge concerning infection of the blood forbids us to believe. Except in experimental cases we cannot conceive that micro-organisms should ever directly gain access to the blood. However small, there must be some local lesion in the tissues by which the micro-organisms gain entry to the system, and from which, as a primary focus, the blood is invaded later. In these cases of apparently primary ulcerative endocarditis we must assume that at some time or other a primary superficial focus must have existed, though it may never have been recognised or may have been forgotten.

There are two possible ways in which these cases may be explained. (1) It has been said that an infective endocarditis is probably, in the majority of cases, superposed upon an old simple valve lesion, and since even in simple valvular lesions micrococci are often present, it is possible that in some cases a local exacerbation of the valve disease takes place and that the formerly simple valve lesion becomes directly ulcerative. (2) It was shown by Becker that when pyogenetic micro-organisms are circulating in the blood, abscesses are formed where tissues are in a condition of lowered vitality or have been injured. Thus, after having injected such micro-organisms into the circulation, he fractured subcutaneously certain of the animal's long bones and found that abscesses were formed at the seats of fracture. It is probable that in the same way a valve affected with chronic disease offers a lower resistance to any pyogenetic micro-organisms that may be circulating in the blood. But it is not necessary that the micro-organisms causing an ulcerative endocarditis should have first gained access to the body immediately before the endocarditis manifests itself. We do not know yet how far micro-organisms may remain in the body in what may be termed a latent condition. Possibly the bacteria which ultimately cause an ulcerative endocarditis may, in certain cases, have entered the body long previously by some superficial lesion and have been hidden away in some tissue without giving rise to symptoms owing to their low order of virulence, though they are nevertheless able to start active disease in an injured part when a cause intervenes whereby they gain access to the general circulation.

We shall not discuss here the fever, diarrhœa, albumosuria, glycosuria, and other symptoms which are or may be met with in patients in whom persistence of irritant action has led to suppuration and allied conditions; these phenomena will be more appropriately considered under special headings. But it may briefly be said that absorption into the circulation, either directly through the capillaries or indirectly by way of the lymphatics, of the chemical products of bacterial action leads to modified exercise of function on the part of many organs and tissues. Probably also similar but less-marked results are produced by absorption of the soluble portions of dead and disintegrated tissue elements, even when solution has not been brought about by bacterial action, but on this point we have at present little or no definite information.

B. **Gangrene and Allied Conditions.**—The other group of changes which results from persistence of irritant action—gangrene and allied conditions—is of a somewhat different order. In all cases irritant action is associated with degenerative changes of tissue elements, and these changes may vary from so slight a condition that recovery of the tissue is possible, to conditions so severe that large tracts of tissue are killed outright. Cases in which degenerative change is very slight do not come within the category of pathological sequels to inflammation, for it is obvious that when the degeneration is slight the irritant must be slight also, and, in particular, its action must not persist.

Where the degenerative changes are severe, one must distinguish between the results of irritant action according as the irritant is so severe that it kills the tissue directly (in which case the dead tissue is called an "eschar"), or as death of the tissue follows persistent action of a somewhat less intense irritant and is really due to the pressure effects of the exudation, etc., to which that irritant has given origin. In the latter case death of the tissue in question is due rather to simple starvation from interference with the blood-supply than to direct irritant action, and though it is a true sequel of inflammation it is comparable with the gangrene which occurs in a part whose blood-supply has been cut off by ligature of the nutrient arteries. Nevertheless, when a tissue has been brought into a devitalised condition by the direct action of an irritant, a smaller interference with the blood-supply will bring about its death than would have been necessary had the tissue been in a normal state.

Death of tissues brought about in this manner is usually termed "gangrene" or "necrosis," and the dead portion of tissue receives different names according as it consists of soft tissues or of bone; in the former case it is called a "slough," in the latter case a "sequestrum."

The term "necrosis," too, is frequently, but not invariably, restricted to death of bone or cartilage, but "gangrene" is used to cover death of a part in which these tissues are involved. For example, a member such as the foot undergoes "gangrene," though cartilage and bone are concerned in the death as well as muscle, skin, and other soft tissues, but in referring to the cartilage and bone in the same "gangrenous" foot, the word "necrosis" would be employed. "Gangrene," "necrosis," "slough," "sequestrum" refer to death of tissue *en masse*; where the dead tissue does not form a macroscopic quantity but is broken up into microscopical fragments, the condition, if it concerns soft tissues, is called "ulceration," and if it concerns bone, is called "caries." The essential point about all these terms is that death involves masses of cells and not individual cells.

Gangrene may be induced in many different ways, and will be more conveniently considered along with the pathology of nutrition than along with inflammation, especially as the varieties of gangrene and the changes undergone by a gangrenous part, which have also to be mentioned, do not really concern us at present. Moreover, for the death of tissue in mass, persistence of irritant action is only of importance by inducing purely mechanical conditions which conceivably might be produced by irritant action, if sufficiently severe, without persistence. The exudation, for example, poured out into the inflamed ear of a rabbit, may produce gangrene, whether that exudation has been poured out rapidly or slowly, if only it is poured out in sufficient quantity. But with ulceration and caries the case is different. Here persistence of irritant action is essential, and for this and other reasons, ulceration and caries come very closely in contact with suppuration and abscess-formation.

(i.) **Ulceration.**—Whenever an irritant has acted upon a superficial tissue, whether cutaneous or mucous, and has led to death of the superficial layers including the papillæ of the corium, inflammation takes place in the deeper layers. After a shorter or longer time the dead tissue is removed, whether it is cast off as a slough or is removed piecemeal, and a surface denuded of skin or epithelium, and of varying extent and depth, is exposed. Such an exposed area is called an "ulcer," and the process whereby the dead material, at first organically united with the living tissue, is separated therefrom is called "ulceration."

In describing the process of ulceration, it is advisable to bear a specific instance in mind, and for this purpose the changes that take place in a Peyer's patch during typhoid fever are very suitable. In this disease typhoid bacilli gain access to the Peyer's patches of the ileum and there lead to inflammatory changes which, aided by the direct action of the poison locally elaborated by the typhoid (and perhaps other) bacilli, cause death (gangrene) of the mass of lymphoid tissue which constitutes the Peyer's patch. From this time forth the patch is a foreign body organically attached to the intestinal wall. It is therefore an irritant quite apart from the fact that it contains within itself typhoid bacilli and their toxin, and that, being dead tissue, it is rapidly invaded by the putrefactive micro-organisms, of which the intestinal contents hold large numbers. From the nature of the case, its action as an irritant upon the deeper layers of the intestinal wall is persistent. Now we have already seen that persistence of irritant action leads to an inflammation that ends in pus-formation, and that this is especially the case when the irritant is bacterial. Such an inflammation occurs in the intestinal wall, and since only living vessels and cells can enter into the actual production of an inflammation, it follows that the seat of the inflammation is the living tissue beneath and around the dead Peyer's patch. So also the seat of actual pus-formation is found where the irritant is of greatest intensity, viz., at the junction of the living with the dead tissue. When the most superficial layer of inflammatory tissue—that in which the changes are most advanced—has broken down into pus beneath the whole extent of the necrosed Peyer's patch, the slough is detached and passes away with the intestinal contents, at the same time leaving bare the uppermost layer of the living but inflamed tissue of the intestinal wall as the floor of a "typhoid ulcer."

The actual separation of the slough, therefore, takes place at the expense of living tissue. It is not the necrosed Peyer's patch which undergoes inflammation nor the Peyer's patch that forms pus, any more than it is the lead which undergoes inflammation or forms pus when suppuration occurs round a bullet that has lodged in the body. But in the living tissues around the irritant afforded by the slough there is formed a zone where inflammation persists and where pus is produced by a liquefaction of the infiltrated tissue lying next to the slough. In ulceration this liquefaction is always carried out by living phagocytic cells, and though the phagocytes penetrate into the slough, and in some degree remove it also by their digestive action, they more commonly succumb to the poisons there present. This zone of inflammation in which pus is being produced is usually called the zone of "separation" or the zone of "demarcation."

Separation of a mass of dead tissue proceeds from the edges inwards. This happens, probably, because at the edges bacterial action is more pronounced, and therefore the tendency to pus-formation on the part of the still living tissues is greater. This point may be very well observed in the separation of a gangrenous mass, such as a toe or foot. At the junction of the dead and living tissues, but formed principally, if not entirely, at the expense of the living tissues, there is found a deep trough in which there is a small quantity of pus. As this trough becomes deeper and deeper, separation of the gangrenous mass advances until at last the whole mass is cast off. It is hardly necessary to remark, that the rate at which separation proceeds depends to a very large extent upon the density of the tissue concerned. Thus, in gangrene of the foot, skin or muscle is divided far more rapidly than bone or tendon; nevertheless, in the case of all these tissues, the process is essentially the same one of ulceration.

Where the mass of dead tissue is very small, and particularly where it is aseptic, as when an infarct results from the lodgment of an aseptic embolus, the changes induced are different, in so far that they are not so marked, but here also the dead material is removed in the vast majority of cases, and by the agency of living cells with the co-existence of inflammation.

When an aseptic embolus, for example, lodges in the kidney, a cone-shaped area of tissue dies, and being dead, it acts as an irritant, though no doubt a very mild one, upon the surrounding tissues. Nevertheless it induces inflammation in its immediate neighbourhood, and a section of such an infarct shows that, though it itself may be bloodless and pale, it is surrounded by a narrow hyperæmic zone, in which, microscopically, signs of inflammation may be observed. As the result of persistent action of the irritant, wandering cells collect in the inflammatory zone; but since the irritant is very slight, and above all is aseptic, the inflammatory material does not break down into pus, but the phagocytic wandering cells of all kinds invade the necrotic cone of tissue and gradually break up and remove every particle of the infarct. At the same time, reparative tissue—the nature of which we shall consider later—invades the cone also, and ultimately not a vestige of renal substance, even in a degenerated form, can be found at the seat of the infarct. In its place there is only fibrous tissue.

In some cases, however, where the aseptic mass of dead material is very large, fibrous tissue does not replace the whole mass, but only its marginal portions, and then the central degenerated mass of dead material may lie, innocuous, in a fibrous capsule for an indefinite length of time.

It has been said above that the floor of a typhoid ulcer is formed by the uppermost layer of the living inflamed tissue of the intestinal wall. This statement needs some little qualification, for though the base of a typhoid or any other ulcer at the moment of separation of the slough consists of inflamed tissue normal to the part, this is only so for a time. After an ulcer has existed a certain length of time, it is found to have undergone different changes, according to the conditions under which it is placed. These changes we must now consider.

When discussing abscess-formation we saw that around the margin of the abscess, at a varying distance from the actual pus, there is a zone of potential repair. A similar zone exists beneath the floor of an ulcer, and for the same reason that it occurs around a purulent focus. The changes, too, that go on in the two cases are identical. Either the zone of potential repair beneath the ulcer becomes a zone of actual repair, in which case the floor of the ulcer ultimately consists of what we shall hereafter describe as "granulation tissue"—this occurs if the irritant ceases to act, or if its intensity is below a certain level; or else, if the irritant be intense, and persist, or if the vitality of the tissue have been greatly diminished, the zone of potential repair becomes a zone of inflammation, which in its turn breaks down, and the ulcer increases in depth and extent. When this takes place in an ulcer of such a viscus as the intestine, stomach, etc., the thickness of whose walls is limited, complete perforation of the wall ultimately ensues, with consequences of varying importance and severity, into the determining factors of which we cannot now enter. As a matter of fact, under ordinary circumstances, irritant action is never absent from the tissue forming the floor of an ulcer, and the irritant being, in the vast majority of cases, bacterial in nature, the floor of an ulcer is seen to be covered with a more or less well-marked layer of pus. This formation of pus on an ulcer persists until, in the process of repair, growth of epithelium has completely covered the floor of the ulcer. In a few cases irritant action and resistance of the tissues are so evenly balanced, that the ulcer apparently undergoes neither extension nor repair; it is then known as an "indolent" ulcer.

In the process of ulceration quite an especial group is formed by those cases in which the vitality of a tissue is markedly lowered, and in which this, rather than the intensity of the irritant, is the essential condition upon which death of tissue and formation of an ulcer depend. Thus, when the saphena vein is varicose, interference with nutrition of the skin of the leg in the neighbourhood of the ankle—where the circulation of blood is normally somewhat poor—is frequently such that, as the result of a slight injury, there occurs necrosis of skin and the formation of a "varicose ulcer." Of the same type, probably, though brought about in a different way, are the gangrenous ulcers that constitute "bed-sores."

Sometimes the lowered vitality is due to severance of the tissue from its nervous supply. Bed-sores of a particularly acute onset frequently follow disease or injury of some part of the nervous system, whether brain or spinal cord. This fact points to an association of nervous change with ulceration, evidence for which is also given by the "perforating ulcer" of the toe which occurs in "tabes dorsalis," a disease in which the postero-external and the postero-median columns of the cord undergo degeneration. It will be remembered, too, that in the last chapter mention was made of the part played by the nervous system in influencing the course of an inflammation. Apparently removal of nervous influence modifies the vitality of the tissues involved whereby their resistance to irritants is lowered. That which to normal tissue would be a stimulus or a slight irritant, to them is a severe irritant.

*Gastric Ulcer.*—In the stomach a somewhat peculiar form of ulceration occurs, which affects so many persons, and the pathology of which is so debated, that it may be mentioned separately. The ordinary "perforating" or "chronic" ulcer of the stomach is commonly seen in two classes of person, anæmic young women and elderly persons addicted to alcohol; it is peculiar in that it has a seat of marked predilection in the stomach, being, in a large majority of cases, single, and situated in the lesser curvature and on the posterior wall of the organ. Its appearance is characteristic, for it is shaped like a funnel, and its wider circumference, which corresponds with the mucous membrane of the stomach, has clean-cut edges.

The question as to the pathology of gastric ulcer is closely bound up with the question why the stomach does not digest itself normally. Many attempts have been made to explain this difficulty. It has been ascribed to the mucus which is perpetually being poured out over the mucous membrane (Claude Bernard, Harley), to the alkalinity of the blood which permeates the mucous membrane (Pavy), to the living condition of the epithelium covering the stomach. Of these explanations probably the last, indefinite though it is, is nearest the truth. For Matthes found experimentally that proteolytic solutions are incapable of digesting living tissues; thus he placed a live frog in a weakly alkaline solution of trypsin at 25° C. for some long time, and found that it was quite unaffected, except so far as the outer cuticle was concerned, which, being dead, was completely digested.

The appearances of a gastric ulcer recall the shape of an infarct, and one of the earlier explanations of the pathology of gastric ulcer was that an embolus is carried into one of the terminal branches of the gastric artery. These terminal branches being end-arteries, it was assumed that a cone-shaped mass of tissue undergoes necrosis and is digested by the gastric juice. This view was adopted by Panum and by Cohnheim, both of whom investigated the question experimentally, Cohnheim by injecting lead chromate directly into the gastric artery after introducing the cannula used for injection so deeply that he involved vessels supplying the mucous membrane only. After a few days he found large ulcers with sloping edges in the stomach. Pavy advanced a slightly different view. He obtained ulcers after ligature of branches of the gastric artery, when the contents of the stomach were made hyperacid, and ascribed the ulcer-formation to auto-digestion of the stomach combined with changes in the vessel walls.

It is true that pathological conditions of the arteries have been found along with gastric ulcer, but in spite of this fact and the fact that Virchow pointed out, and Hoffmann confirmed, the frequent occurrence of arterial changes in chlorosis, the views that the ulcer is due to embolism, and that it depends upon pathological changes in the gastric end-arteries, are by no means satisfactory. Still less so, perhaps, is the so-called "spastic" view taken by Klebs and by Axel Key, according to which spasmodic contraction of the muscular tissue, either in the walls of the arterioles (Klebs) or in the walls of the stomach (Key), produces local anæmia and death of portions of the gastric mucous membrane.

Matthes finds that the hydrochloric acid of the gastric juice acts as a protoplasmic poison on cells, but that the effect shown by the cell varies according to its nature, nutritive condition, etc. Some cells are not injured at all, some suffer very severely. If, then, under conditions of which we are ignorant, the acidity of the gastric juice becomes increased (and that this sometimes occurs is certain), or if the resistance offered by the cells composing the gastric mucous membrane to the normal acidity of the gastric juice becomes diminished, the cells are killed over a certain area, and then are readily digested by the proteolytic ferment. Whether this be the true explanation of the commencement of a gastric ulcer or no—and there are certain difficulties in the way of its acceptance as a full explanation—in all probability the chronicity of a gastric ulcer is in part due to a hyperacid reaction of the gastric contents. For Matthes found experimentally that a simple ulcer, when exposed to a degree of acidity such as is developed during digestion, readily becomes converted into a chronic ulcer. Some part, however, must be played by the constant movement and other irritation to which the ulcer is, from the nature of the case, always subjected.

It follows from what has been said that the pathology of gastric ulcer must, in many respects, be unlike the pathology of ulcer in other parts; in particular the method whereby the slough is removed is unique. Nevertheless, once the gastric ulcer has been formed, the changes which it undergoes are similar to those undergone by any other ulcer, for a gastric ulcer may heal or it may extend. If it heals, it does so with the formation of a true cicatrix; if it extends, it may perforate. That extension is accompanied by pus-formation is shown by the fact that abscesses behind the stomach following on gastric ulcer are not very rare. The absence of pus on the surface of a gastric ulcer is certainly due to the rapidity with which pus is removed after it has been formed.

(ii.) **Caries.**—Caries of bone—or, as it is also often called, "rarefying osteitis"—differs only from ulceration of soft parts in respect of those points which depend upon the nature of the tissue in which the inflammatory process is going on. Since the blood-supply of bone is less than that of soft parts generally, and since, owing to the deposition of calcium salts, the hardness of bone is one of its most characteristic points, it follows that, *cœteris paribus*, dead bone can be removed less rapidly than dead but soft material. Hence caries of bone is a long process. Moreover, solution of the organic basis of bone, so as to bring about separation of the living from the dead tissue, is impeded by the presence of the calcium salts along with the organic matter. These calcium salts must be dissolved also, and in this point lies the only real difference between caries and ulceration.

In caries of bone the same formation of granulation tissue takes place that we have seen to take place in ulceration. Similar elements are employed in the process, though some confusion is created by the fact that different names have been given to certain of the cells concerned, and similar results take place in the surrounding tissues.

We will assume that a portion of the outer surface of the shaft of the tibia has undergone necrosis. At first it is organically in connection with the still living bone, just as the slough is at first organically in connection with the deeper parts of the intestine when in typhoid fever the inflamed Peyer's patch undergoes necrosis. In both cases the dead material acts as an irritant to surrounding parts, and leads to inflammation; but whereas in the Peyer's patch inflammation can show itself markedly beneath the dead material, in bone this can only occur to a limited extent, and the region where inflammatory changes are recognised in this case is the periosteum surrounding the portion of dead bone. This limitation of the area over which inflammation can develop to any great extent is another important cause for the chronicity of the process of separation of the sequestrum. Nevertheless, in the periosteum inflammatory changes occur, with the accompanying hyperæmia, exudation of fluid, and migration of wandering cells, and around this zone is a zone of potential repair.

Now, just as in the case of the Peyer's patch separation of the slough is carried out at the expense of the living tissues, so separation of the sequestrum is carried out at the expense of the living bone. The wandering cells in both cases have digestive functions, and since digestion by phagocytes is accompanied by the formation of acid, the calcium phosphate and carbonate, of which bone is so largely built up, can be dissolved by phagocytes, though necessarily the process is a slow one. The directions in which phagocytic cells can wander are also mechanically limited to the Haversian canals, and since the phagocytes can only attack the bone surrounding these canals by erosion from the outside, they come to form a more or less complete lining to the canals. In process of time they dissolve the calcium salts and digest the bone in their immediate neighbourhood, so that the Haversian canals become irregularly widened, and the individual phagocytes lie in small depressions or pits which they have themselves formed. These depressions are identical in mode of formation with the depressions known as Howship's lacunæ or foveolæ, which are found in an ordinary growing bone, and the phagocytic cells which lie in the foveolæ have similar appearances in both cases and the same function. In both cases, too, they are called "osteoclasts," but in normal bone by many authors they are called "myeloplaxes."

Osteoclasts have different appearances to the cells which we have hitherto described as wandering and phagocytic cells. They belong to the class known as "giant cells," of which mention will be made hereafter. As to the phagocytic properties of giant cells in general there is little doubt, and there is no doubt whatever that some kinds of giant cells (and osteoclasts in particular) are markedly phagocytic. We must therefore regard osteoclasts as identical in characters and in function with the giant cells present in other varieties of inflammation or its sequels.

When the osteoclasts have done their work, the dead bone is separated from the living bone, and an irregular surface of living but inflamed bone is left which corresponds to the floor of a typhoid ulcer. But just as in the case of a typhoid ulcer a zone of potential repair exists at some distance from the slough, so in the case of necrosis of bone at some little distance from the sequestrum there is a zone of potential repair in the periosteum. Here the young bone-cells (osteoblasts) are in a state of proliferation and high activity, as in the other case the young connective tissue cells (fibroblasts[1]) are in a state of proliferation and high activity. Assuming that the irritant action does not extend, just as granulation tissue is produced in the latter case in this zone of potential repair, so it is formed in the zone of potential repair in the former case. And just as the process in the neighbourhood of the typhoid ulcer ends in the formation by the fibroblasts of their normal final product (fibrous tissue), so in the neighbourhood of the bone ulcer, *i.e.*, the carious focus, the process ends in the formation by the osteoblasts of their normal product (bone). Assuming, on the other hand, that the irritant action extends, the results in both cases are again similar, for just as in the typhoid ulcer the inflamed but still living tissue of the intestinal wall breaks down and the ulcer extends, so in the disease of bone the still living but inflamed bone breaks down and the carious patch extends.

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[1] Perhaps under the term "fibroblast" ought also to be included young endotheloid cells; upon this point see below, p. 348.

(iii.) **Comparison of Ulceration with Caries.**—The processes at work are therefore identical. An apparent difference, however, is produced by the facts that the process in the case of bone is not infrequently aseptic, and is always of long duration, whereas in the intestine the process can never be aseptic and commonly is of relatively short duration. Hence in the intestine less of the reparative process is seen along with the presence of an ulcer than is seen in the bone when caries is still going on. Indeed the new formation of bone in the neighbourhood of a carious focus is often remarkable, but the new formation of fibrous tissue in the case of a typhoid ulcer is practically restricted to the amount necessary for filling up the vacant space. But even here the difference is apparent only and not real, for in the repair of any ulcer more fibrous tissue is at first present than is necessary, and the excess is gradually removed after repair is complete, and in the repair of bone, though bone is at first produced in obvious excess, this excess is also gradually removed after repair is complete.

Another apparent difference between the two processes we have considered is brought about in the following way. The broken-down material and the slough in the case of a typhoid ulcer are carried into the lumen of the intestine, and pass away with the intestinal contents, but in the case of necrosis of bone this cannot occur, unless the seat of necrosis is open to the external air. Sometimes this is actually the condition, but not infrequently caries of bone takes place without such a communication with the open air, and in these cases the broken-down material and the dead bone must collect at the seat of bone destruction. Under aseptic conditions the amount of broken-down material may be sufficiently small for removal by wandering cells, and a sequestrum may become enclosed in a bony case by a process akin to that which obtains in encapsulation. But when micro-organisms are concerned in the process, an abscess is formed in connection with the bone. The pus formed in these cases "points" as it does in other cases of abscess, and ultimately discharges itself through the skin or into some cavity. The track which the pus has excavated for itself, and which, of course, opening on the surface, leads down to carious bone, receives the special name of "a sinus," but its mode of formation is identical with that track which is produced when an abscess in soft parts has procured its own evacuation. So long as destruction of bone and pus-formation are still going on at the bottom of a sinus, the sinus remains open, though it may temporarily close by the growth of epithelium over the cutaneous surface, or even by coalescence of the walls of the sinus itself over a limited area. The irritation produced in the walls of the sinus by the pus which constantly passes over them, keeps those walls in a state of chronic inflammation, and as a result the walls of a sinus are composed of granulation tissue, the most external portion of which (*i.e.*, that directed towards the lumen) is constantly breaking down into pus. The pus or sero-purulent fluid that exudes from the orifice of a sinus is therefore in part yielded by the bone and in part by the walls of the sinus themselves.

We may now consider the phenomena of repair in detail.

In the lower animals, and particularly in animals unprovided with a hæmal vascular system, repair of a complex tissue is a much more complete process than it is in the higher animals. In the Asteroidea if a member be removed it is completely re-formed, and the same may obtain in the Crustacea. Even among vertebrates, repair of a specialised type is found in certain of the Reptilia. But when we come to the higher Mammalia we find that repair of a complex tissue is practically confined to regeneration of epithelia and of various kinds of connective tissue. With these higher animals alone we are immediately concerned.

V. **Regeneration of Tissues and Repair.**—It will conduce to a clearer conception of the processes involved in *repair* of a complex tissue, if *regenerative* processes be first examined in the different elemental types of tissue.

(i.) **Epithelium.**—In the case of epithelium we have the simplest form of regeneration. The cells composing the deepest or germinal layer divide in a direction parallel to the surface, and thus, by the constant formation of fresh layers from below, the loss of old and superficial layers is made good. This process is, of course, constantly going on in normal life, and when, from some reason, there is a greater removal of epithelial cells, so long as the germinal layer remains intact, repair simply takes place by an increased rapidity of division on the part of the germinal cells. But epithelium cannot be generated except by pre-existing epithelium, so that, if the germinal layer has been destroyed over any area, the surface that is left can only receive a covering of epithelium by growth from the intact germinal layer at the periphery.[1] Under the influence of a stimulus of unusual persistence and of moderate intensity, the formation of epithelium from below may outstrip loss from above and the epidermal layers may become greatly increased in number. If the superficial layers are highly corneous, the thickened layers constitute a "callosity." Inflammation is very commonly associated with prolific growth of epithelium, and in the case of the epidermis, with prolific growth of epidermal structures;

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[1] The tendency of epithelium to grow from the edges is utilised in the surgical operation of skin-grafting. It was found by Reverdin that if small portions of skin, including the germinal layer, be placed on the surface of a wound, not infrequently the vitality of the graft is maintained until it has become organically a part of the tissue with which it is in contact on its under side. It then forms a focus whence the formation of young epithelium proceeds in all directions over the raw surface of the wound. By this discovery the final healing of extensive superficial wounds has been materially shortened.

the growth of hair or of nails in the neighbourhood of a part that has long been the seat of chronic inflammation is often remarkable. The reason of this overgrowth, of course, lies in the increased amount of nutriment supplied to the parts by the active hyperæmia and the exudation that accompany inflammation. Another very common result of the excessive production of epithelial cells is seen in the prolongation of the interpapillary processes into the corium in the immediate neighbourhood of the inflammatory focus.

In the repair of epithelium its essential type is never changed; a spheroidal cell never becomes columnar or squamous, a squamous cell never becomes spheroidal. Nevertheless there is commonly some departure from the usual form; squamous cells, for example, derived from a rapidly proliferating epithelium are neither so compressed nor is their shape so regular as when derived from normal epithelium, and spheroidal cells under similar conditions generally become polyhedral from mutual pressure. The complex papillæ of the true skin are never re-formed when once they have been destroyed, and it is the absence of papillæ which gives their characteristic smooth appearance to the epidermal layers covering an ordinary scar.

(ii.) **The Connective Tissues.**—Regeneration of the connective tissues forms the most important portion of the subject of repair, for with the exception of epithelium, repair of all parts in which the tissue elements have been destroyed is carried out in the main if not entirely by the new formation of one or other member of this group. The law, that less highly specialised tissues are regenerated more easily and more completely than more highly specialised tissues, holds good here also, for the new formation of simple fibrous tissue is far more common than regeneration of the more highly specialised bone and cartilage. There is a certain amount of interchangeability amongst the members of this group of tissues, but it lies rather in the replacement of a higher form, such as cartilage, by a lower form, such as simple fibrous tissue, than in the opposite condition. In fact the formation of cartilage or bone in the repair of an injured simple fibrous tissue is unknown, whereas the repair of injured bone or cartilage by the new formation of fibrous tissue is not uncommon. In this respect cartilage seems to be a more highly specialised substance than bone, for when cartilage has been destroyed as the result of irritant action, new cartilage is not formed, whereas when bone has been destroyed the cell proliferation which takes place in the periosteum preserves its characters and new bone is ultimately formed. But this new bone is not formed through an intermediate cartilaginous stage, even though the original bone may in embryonic life have been laid down in that substance. It is produced by a direct ossification of the calcified periosteal fibrous tissue, and the osteoblasts play the same part in new bone-formation that fibroblasts play in new fibrous tissue formation.

*Fibroblasts.*—A part in which the formation of young fibrous tissue is taking place shows the presence of large numbers of young connective tissue corpuscles or fibroblasts. These cells, when their nature is beyond question, appear as large fusiform cells with abundant protoplasm, which tapers towards the two poles or may perhaps bifurcate at one extremity or both. The protoplasm stains very faintly and commonly appears hyaline or slightly granular. The nucleus is an elongated, fusiform or oval or rod-shaped body, relatively poor in chromatin and staining faintly though more deeply than the protoplasmic body of the cell. Karyokinetic figures in the nucleus are frequently to be observed. Between individual cells may usually be seen a few strands of fine wavy connective tissue.

When the process is more advanced these cells diminish in numbers, their protoplasm becomes more scanty, their nucleus more elongated and angular and stains more darkly, karyokinetic figures become rare, and the amount of definite fibrous tissue between the cells becomes greater. As time goes on, these features become more noticeable, until at last connective tissue of a type scarcely, if at all, differing from normal connective tissue results, and the nuclei of such fibroblasts as remain are represented by nuclei of the connective tissue corpuscles. The process in the case of repair of bone is exactly similar in all its essential details, though of course deposition of calcium salts in the bodies of the cells and in the fibrillar network is superadded.

Now though these features may easily be made out in any healing wound, or, indeed, in any part in which repair is taking place, the steps in the process have been and are a subject of great discussion. The two cardinal points upon which there is disagreement are, firstly, the origin of fibroblasts, and secondly, the method whereby fibroblasts form connective tissue. Concerning each of these points a few remarks must be made.

*The Origin of Fibroblasts.*—When inflammation first of all became the subject of exact investigation, it was held that the new tissue which ultimately appears is formed at the expense of the exudation and that the fibrin-formation which is so generally evident in inflammatory exudations is the first step in the process. For this reason such varieties of inflammation as terminate in the formation of fibrous tissue were called "plastic" inflammations, and the fibrin which formed in the exudation in such cases was called "plastic" or "formative lymph." But after Virchow in 1855 formulated his famous dogma, *Omnis cellula e cellulâ*, the old view that connective tissue and connective tissue corpuscles in repair are formed from the exudation gave way to cellular theories.

(*a*) *Hæmal Theory.* — Of these cellular theories one was strongly supported by Cohnheim and others, who regarded the fibroblasts as being derived from hæmal leucocytes. This view was largely based upon an experiment originated by Ziegler. Ziegler placed small oblong chambers (made by fastening two cover-glasses at the four corners in such a way as to leave a small space between them) under the skin of the dog and left them for varying lengths of time. The space between the glasses became filled with cells which could be directly examined under the microscope. The cells present in chambers that had not long been allowed to remain in the subcutaneous tissue contained, besides fibrin and red blood-corpuscles, numbers of colourless blood-corpuscles, many of which were fatty and resembled pus-cells. In chambers that had remained in the subcutaneous tissue about five days, cells larger than the above first began to show themselves. These cells in their characters were intermediate between the colourless blood-corpuscles and the "epithelioid" cells, whose appearances are similar to those which have already been given for fibroblasts, and the existence of which in the chambers was first recognisable by about the seventh day. By about the tenth or twelfth day the presence of large multinuclear cells—the so-called "giant cells"—was noted, and in a chamber at this date, leucocytes, epithelioid cells, giant cells, and transitional forms between all of these were recognisable. Certain of the cells seemed to grow at the expense of other cells, so that the more numerous the epithelioid and giant cells the less numerous the leucocytes, and it was in this way that Ziegler explained the formation of epithelioid and giant cells. These observations were taken as furnishing experimental proof that migrated white blood-corpuscles are capable of further development and are the primary source of the new fibrous tissue which is found in repair.

But this view of Cohnheim and Ziegler was from the first received with a certain amount of opposition, and the subsequent work of a large number of investigators has tended to strengthen the opposition to such an extent, that even Ziegler has at the present time altered his opinion and holds that connective tissue is only formed from connective tissue.

(*b*) *Connective Tissue Theory.*—The other cellular view concerning the origin of fibrous tissue in repair is, that fibroblasts arise from pre-existing connective tissue corpuscles. That this is true there can be no doubt, for the changes that were described by Leber in the corneal corpuscles after inflammation of the cornea are conclusive, and the evidences of cell division seen in connective tissue on the borders of an area of inflammation are equally unmistakable. But whether this view is entirely to replace Cohnheim's view, it is difficult to say, especially when we consider that in all reparative tissue that is on the way to become fibrous tissue—the so-called "granulation tissue"—there are present large numbers of round cells with faintly staining nuclei and a fairly large amount of protoplasm, whose appearances are in every respect similar to those of hyaline wandering cells found in the blood. It is possible that these uninuclear cells in the blood are really derived from connective tissue, and that when they are found in developing connective tissue they have only returned to their original home; it is possible that these uninuclear cells in connective tissue are quite distinct in origin, nature, and function from ordinary connective tissue corpuscles; it is possible that they are developed from the finely granular oxyphil cells which migrate in so large numbers from the blood-vessels in inflammation, and the phagocytic and amœboid nature of the uninuclear cells is well in accord with such a view; it is possible that in sections many of them are artefacts, for transverse section of a fibroblast through the nucleus would yield the appearance of a uninuclear hyaline cell. Upon none of these points have we satisfactory information, so that until the origin and fate of the uninuclear cells seen in granulation tissue is decided, it is impossible to deny that some of the fibroblasts may be derived from leucocytes, or to assert that the connective tissue formed in repair is derived from pre-existing connective tissue alone. We can, however, affirm with comparative certainty that pre-existing connective tissue corpuscles play a considerable part in the process.

The view that the cells concerned in repair are fixed tissue cells is largely bound up with the name of Stricker. At a time when Cohnheim was putting forward his view that the cells concerned in inflammation and repair are leucocytes, Stricker as vehemently was maintaining that, as the result of irritant action, the tissues of a part, whatever their nature, return to an embryonic condition, or in other words, that they again become converted into cells, and again show a marked tendency to proliferation. Just as for Cohnheim all cells in any inflammatory or reparative process were at bottom leucocytes, so for Stricker all cells in such processes were tissue cells that had reverted to an embryonic condition. Each of these authors, however, was too dogmatic and exclusive, and as Cohnheim erred in holding that repair depends exclusively upon further development of leucocytes, so Stricker erred—and to a greater extent—in denying any part to the leucocytes in pus-formation. The solid importance, however, of some of Stricker's work is overlooked partly because of the bitterness of his attack, and partly because of the brilliance of his opponent.

A view which in some respects is akin to that of Stricker has been of late years elaborated by Grawitz. According to this author, there are present in ordinary connective tissue numbers of "Slumber cells (Schlummerzellen)" which under normal conditions are invisible, but which "awake" under the influence of a suitable stimulus and then are recognisable in stained specimens. With their "awakening" the cells take on active properties, so that they again wander, proliferate, and form connective tissue as before they "slumbered." The fact that Grawitz's slumber cells are invisible reduces this view from a theory to a mere poetical conception. Nevertheless it is well to bear in mind that though, with our present methods, we may be unable to recognise the existence of cells in any part, it does not necessarily follow that no cells are present. The revelations made by Golgi's method in the histology of the nervous system are sufficient to teach us caution in this respect.

*Origin of Fibrous Tissue from Fibroblasts.*—Concerning the method whereby connective tissue is formed from fibroblasts, discussion has been far less animated than concerning the origin of the fibroblasts themselves. Upon this subject also there are two chief views. According to the one, strands of fibrous tissue are formed by the splitting off from the protoplasm of the fibroblast of peripheral layers in the direction of the long axis of the cell. According to the other, fibrous tissue is produced by a modification of some substance secreted by the fibroblasts. Upon this point Sherrington and Ballance write as follows:—"We were unable to satisfy ourselves on the question as to whether the fibrillated extra-cellular matter had been formed by direct transformation from the surface portion of the cell body, or whether it had arisen as a secretion from the protoplasm of the cell. But the latter view seems to us the more probable, if only for the reason that the fibroblast cell and its new capsule of fibrillated matter are, when taken together, much larger than, so far as we have observed, the individual naked fibroblast ever is."

*Endothelium.*—Repair and proliferation of endothelium must probably be considered quite apart from the epithelia and more closely in connection with the connective tissues. Upon this subject our information is as yet inconclusive, but there is reason to believe that endothelial cells like connective tissue cells are embryologically of mesodermal origin. In the processes constituting repair, it is certain that proliferation of endothelial cells, whether of lymphatics or of blood-vessels, plays a very prominent part, and there is high probability that such endothelium as is present in fully repaired tissue is derived directly from pre-existing endothelium. But at certain stages of their life-histories, and especially when rapid proliferation is taking place, it is impossible by any of the means at our disposal to distinguish endothelial cells from fibroblasts derived from connective tissue corpuscles, and hence it is impossible to say whether any part in repair other than the formation of endothelial linings for new blood-vessels is carried out by these cells or no. It is by reason of this similarity of appearance and doubt as to origin that the terms "fibroblast," "connective tissue corpuscle," "endothelioid cell," "epithelioid cell" are so frequently used interchangeably in descriptions of inflammation, even by one and the same author.

The most important process in repair with which we are acquainted in which proliferation of endothelium plays a part is the new formation of capillary blood-vessels. It is clear that for the nutrition and for the further development of such proliferated cells as are destined ultimately to form the repair tissue, a sufficient supply of blood is necessary. At an early stage, when the proliferated cells are relatively few in number, that nutrition may be carried out by means of the exudation from the pre-existing congested blood-vessels. But there is a limit up to which this is possible, and at a certain point, unless fresh methods are adopted for the supply of nutriment, further development must be arrested, and in all probability more or less marked degenerative changes will take place in the young cells. This additional supply of nutriment is carried out by the formation of new blood-vessels which permeate the rapidly proliferating tissue.

*Formation of New Blood-Vessels—"Granulations."*—If a healing ulcer be examined it will be noticed that the surface of the wound is covered by a number of red projections, each about the size of a pin's point. These projections are minute blood-vessels, and their number and the thinness of their walls are readily evidenced by the smart bleeding that occurs if the surface of the ulcer be subjected to even a slight degree of rough treatment. It is from the presence of these "granulations" on the surface of such a healing part that the tissue which is destined to repair the wound is called "granulation tissue."

If a microscopic section be made of such a granulating wound at right angles to the free surface, it will be seen that a large number of capillary blood-vessels run in more or less parallel lines from the deeper parts to the surface of the wound. These capillaries do not fully reach the surface, but are covered either by a small amount of fibrin or by a few layers of cells resembling hæmal leucocytes, or by a mixture of both in varying proportions. Nor do they end in free extremities, but immediately beneath the layer of fibrin and cells that has been mentioned they form a complete curve and run in a direction away from the surface. These blood-vessels, therefore, form loops analogous to the loops of Henle in the kidney, and from this fact they are known as "granulation loops." In the depth of the wound these loops may be seen to be continuous with capillary blood-vessels belonging to the uninjured tissues, so that there is no difficulty in arriving at the conclusion that the new capillary blood-vessels in granulation tissue are formed from pre-existing capillaries of the normal parts.

In the embryo Billroth described three methods after which new blood-vessels are formed. In the first of these, solid cylinders of cells closely united to one another are laid down; these cylinders subsequently become hollow by the transformation of the axial cells of the cylinder into blood-corpuscles which are afterwards carried into the circulation. In the second, more or less fusiform cells arrange themselves in such positions as to enclose spaces which are irregular at first but later become converted into the channels of blood-vessels. In the third, solid buds are formed from pre-existing capillaries after the manner described below; these become canalised and finally serve as capillaries. So far as the lumen is concerned, the first and third methods are similar in that the canalisation of the solid protoplasmic masses is considered to be carried out by vacuolation of the central part of the protoplasm, and these methods are generally accepted, but the majority of authors at the present day do not accept the second or inter-cellular mode of formation.

Thoma, however, believes that the lumen in all cases of new formation of blood-vessels is of inter-cellular origin. He acknowledges two varieties of new vessel formation, "primary new formation of vessels" and "new formation of vessels by budding." In his first method, which takes place when the first capillaries are being formed in the vascular area of the embryo, the cells of the mesoblast become arranged in strands in the vascular area. In these strands rounded spaces appear between the cells, and the margin of the cells towards the spaces are more refractile. The spaces, which are filled with a clear, probably fluid, substance, open into one another and thus form the first capillaries of the vascular area, and the cells around the hollow spaces become gradually transformed into pavement epithelium. Thoma's second method of new vessel formation by budding—and this method is practically identical with that described by Billroth—begins in the vascular area as soon as the first capillary network is formed. The protoplasm of the endothelial cells forming the walls of the pre-existing capillaries sends out solid conical buds which grow into long threads; at the same time the nuclei of the endothelium of the capillary wall divide by karyokinesis, so that nuclei are generally to be found in the base of the cone-shaped bud. The long thread-like prolongations of the buds then unite with neighbouring ones and in this way form protoplasmic bridges between different portions of the capillary network. New formative cells not infrequently arise along the side of the buds. The buds then gradually become hollowed out, generally beginning from the lumen of the capillary, to the wall of which they are attached, and the lumen is pushed into the buds in such a way that its sharp outline is always distinguishable. When these processes have been completed in two buds which together bridge over the space between two capillaries, the bridge has become hollow in its whole length, and a new capillary has thus been formed connecting the two old capillaries.

In post-embryonic life this method of new formation of vessels by budding is the only method known. It was studied by various authors and notably by Arnold, who investigated the process in the tail of the tadpole, in the cornea, and in the vitreous humour. A newly-formed blood-vessel is always a capillary. If further development take place and the ultimate result be the formation of an artery or vein, the muscular coat is probably formed by the extension of muscular elements from pre-existing blood-vessels. In the embryo, however, the muscular coat is probably in part formed by a transformation of cells apposed to the sides of the young capillaries. The elastic elements of newly-formed arteries and veins are generally considered as products of the muscular coat.

The arrangement of the young fibrous strands in repair is largely determined by the direction taken by the new blood-vessels, and, judging from the experiments of Sherrington and Ballance, by the lines laid down by the filaments of fibrin formed in the inflammatory exudation. In any healing wound the young fibrous tissue and fibroblasts are to be found arranged in greatest amount and most regularly in the direction of and in the immediate neighbourhood of the granulation capillaries. Consequently, the new strands of fibrous tissue in repair of an open wound, such as a healing ulcer, are principally arranged at right angles to the free surface of the wound. This is only true, however, for the youngest part of the repair tissue, for in deeper and more fully formed reparative fibrous tissue the cells and the fibrous tissue bundles show a much more intricate arrangement; in particular it is common to find that the general direction of the young, highly cellular, fibrous tissue is parallel to the surface of the wound, and, therefore, at right angles to the direction taken by the granulation capillaries.

This disposition of the interlacing fibrous tissue is of very great importance, from the point of view of later changes occurring in the repair tissue. It is a characteristic of fibrous tissue that so long as it lives it undergoes contraction, most rapidly when it is young, less rapidly as its age advances. Now, that the vascularity of the young fibrous tissue in repair is very considerable is shown by the pink or red colour of a recent scar, and the change from the pinkness of a young scar to the dead whiteness of an old scar depends upon the fact that during its contraction the reparative fibrous tissue obliterates a very large proportion of the blood-vessels which were originally present in the granulation tissue. The constant contraction of fibrous tissue is also accountable for the fact that an old scar is commonly depressed below the level of the skin. A very good example of these two conditions is seen in the changes that occur after small-pox. At first, the scars left on the face and elsewhere by repair of the ulcers formed during the course of the disease are red and on a level with the untouched skin in the neighbourhood. But with the lapse of some months, contraction of the reparative fibrous tissue leads to the formation of the well-known white "pits" or "pock-marks" with which the face of such patients as have suffered severely are deeply and permanently scarred.

(iii.) **Muscle, Nerve, Gland.**—In the case of what we may consider to be more highly specialised tissues, such as muscle, gland, and nerve, questions of repair are very difficult. In the case of epithelium and fibrous tissue, repair and regeneration are synonymous terms, but here, at the very outset, we have to distinguish the two processes. For there is no doubt, if a considerable portion of muscle, gland, or nerve substance has been removed or destroyed, that the greater portion of repair is not regeneration, but replacement, since the space left by destruction of any of these tissues is filled up by a tissue different from that which existed in the region originally. In all these cases repair is carried out by an overgrowth of fibrous tissue, and for this reason in the higher animals "repair" comes to be synonymous with "new fibrous tissue formation." Repair of highly specialised tissues in such animals certainly occurs, but whether regeneration occurs is a different matter.

(*a*) *Unstriped Muscle.* — If we consider unstriped muscle, it seems reasonable to expect that when there is destruction, repair should be carried out by regeneration of similar unstriped muscle. We know that unstriped muscle fibres can proliferate, because the changes seen in the uterus, for example, in successive pregnancies, can only happen because, under the stimulus of conception, the latent proliferative power of the muscle-cells is called into play. But as a matter of fact, we find that if a part, such as the uterus, bladder, or intestine, into whose composition unstriped muscle largely enters, be the seat of injury, repair is carried out, not by the new formation of unstriped muscle, but by the new formation of fibrous tissue. We have here a remarkable instance of the fact that the kind of stimulus is important in determining the kind of cell proliferation that shall take place; for as in the uterus, so in the other viscera that have been mentioned, stimuli of a certain kind lead to proliferation of the unstriped muscular tissue. In the same organ one kind of stimulus leads to proliferation of muscle fibre cells, another kind of stimulus leads to proliferation of connective tissue cells.

(*b*) *Striated Muscle.* — Repair of striated muscle also takes place by formation of fibrous tissue, but there is no definite evidence, in spite of assertions to the contrary, that regeneration of striated muscle ever occurs. In this respect there is a difference between the two kinds of muscle, for one must regard the unstriped muscle found in the pregnant uterus and in the newly-formed arteries and veins of scar tissue as having been regenerated.

(*c*) *Nerve.* — The same distinction between regeneration and repair must be made in the case of nerves and glands. If a nerve be divided, and the two ends be brought together, assuming other conditions to be favourable, repair of the wound takes place, and the anatomical continuity of the nerve is re-established by the formation of the necessary amount of new fibrous tissue between the two ends. But re-establishment of functional activity may be long delayed, or, indeed, may never take place at all, and in that case one must conclude that though repair takes place, regeneration is absent. On the other hand, in fortunate cases, physiological continuity of such a divided nerve may in time be fully re-established. How this result is attained is a subject of discussion, but the balance of evidence seems to be in favour of the view that such functional fibres as are found at a later date, in the case of an efferent nerve, on the distal side of the original seat of injury, are produced by direct downward growth of the central ends of the cut axis-cylinders which are in connection with the living ganglion cells, and the nutrition of which is therefore maintained. The reason why the new fibres in the distal part of the nerve lie in the old trunk is probably because they find least resistance in this direction to their growth. Regeneration of nerve, if this view be correct, must therefore be strictly analogous to the formation of unstriped muscle in the case of newly-formed arteries.

(*d*) *Gland.*—Concerning glands the case is yet again somewhat different. If the main bulk of the gland lies in the depth of a mucous membrane strict regeneration may take place. Thus in the female the tubular glands of the endometrium are re-formed every month in spite of the fact that by far the greater part of the total length of each gland is cast off with the disintegrated mucous membrane that is shed at each menstrual period. But the bases of the glands lie not in the mucous membrane but in the muscular tissue, so that there is always in the healthy state of the uterus a certain portion of the gland left from which regeneration can take place. On the other hand, if a portion of such a gland as the mamma be removed, repair and not regeneration follows, or at least is the more obvious condition.

One cannot definitely assert, however, that regeneration of gland substance in such a case as the one last mentioned does not occur, for, according to Ponfick and others, after removal of considerable portions of liver and kidney, a true regeneration of the essential gland substance takes place by division of the still remaining elements. We have to distinguish, however, in the case of glands, the regeneration of glandular epithelium, which is a comparatively simple process, having its analogies with regeneration of epithelium in ordinary life, from the regeneration of glands as composite bodies. The former must be very common and complete, but the latter, we have reason to believe, is very rare and incomplete. It is probably because of the great simplicity of the uterine glands that their regeneration is so readily effected; anatomically, they consist of little else than a single layer of epithelial cells.

*Giant Cells.*—Before proceeding to describe the modes in which repair takes place under different conditions, it is necessary to mention briefly a variety of cell—the giant cell—which is very frequently found in association with the sequels of inflammation, though in the normal body it is only found in red medulla of bone.

Giant cells vary in size; in one case they are perhaps only twice the size of the hyaline cell, in other cases they may be forty or fifty times its size. Their characteristic feature is that they consist of a mass of undifferentiated protoplasm in which is present a variable number of nuclei. The protoplasm is hyaline and shows no intrinsic granules, though as a result of the phagocytic function, to which reference will be made below, foreign particles of the greatest diversity may be found within the cells. Usually in microscopical specimens the cell is separated by a more or less well defined space from the surrounding tissue, but this is probably an artefact, and due to contraction of the protoplasm during the process of hardening. Not infrequently the protoplasm sends prolongations in various directions, so that the outline of the cell is somewhat irregular; indeed a giant cell has no "typical" shape.

The number of nuclei present in a giant cell is no less variable than the size and shape of the cell itself. Sometimes only two or three, sometimes as many as a hundred, nuclei may be seen in a single cell. Generally, however, the number of nuclei in a giant cell seen in a microscopical section varies between about five and twenty. The arrangement of the nuclei is very irregular also; in one case they may be crowded together at one spot, leaving the main body of the cell free; in another case they may be more or less evenly distributed through the mass of protoplasm; and in yet another case they may be arranged for the most part around the periphery of the cell. Giant cells found in tubercular inflammation are roughly characteristic of this variety of inflammation, the nuclei being usually arranged somewhat in the form of a crescent at one end of the cell, and the outline of the protoplasm being rounded at this extremity. The appearance yielded by the cell as a whole is thus often highly suggestive as to the nature of the inflammatory process in which it is present. The nuclei of giant cells may be large or small, oval or round, and may stain deeply or faintly.[1]

Giant cells may be found in any variety of inflammation, but they are especially common in inflammation of bone, in tuberculosis, and in actinomycosis, facts which suggest that chronicity of inflammation plays some part in their formation. According to Sherrington and Ballance's experiments on the guinea-pig giant cells were found in the glass chambers used (see below) three days after the chambers had been inserted into the subcutaneous tissue. In the dog, under approximately similar conditions, Ziegler did not find them until about the tenth or twelfth day.

There is some doubt as to the manner in which giant cells are formed. They may apparently either be produced by fusion of the protoplasm of many cells, the nuclei remaining distinct, or by repeated division and subdivision of the nucleus of one cell, the protoplasm of which does not segment as in normal cell proliferation. Judging from analogy, the former method would seem to be the more probable, for the formation of plasmodial masses by wandering cells may readily be observed outside the body in a hanging drop, in which, besides the wandering cells, bacteria are also present. Whether the presence of many nuclei in undifferentiated protoplasm is to be regarded as a sign of weakness of the cell (Weigert) or as the sign of a reaction to a powerful "formative" stimulus (Virchow), it is difficult to say, but according to Weigert many of the nuclei in the periphery of the cells are dead or degenerated.

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[1] In some cases appearances very similar to those presented by giant cells are pure artefacts, as, for example, when either a lymphatic or a capillary blood-vessel filled with solid but amorphous substance is seen in transverse section. There is then found a central slightly granular mass, around which is arranged a more or less regular layer of endothelial nuclei. If the nuclei, owing to localised proliferation of endothelium, are heaped together at certain spots on the periphery, it may be almost impossible to determine with certainty whether such an appearance is a true giant cell or no.

As to the nature of the cells concerned in the formation of giant cells there is also some doubt, but most probably they arise from the fixed tissue cells, using that term in the broadest sense. Arnold, however, believes that they are of hæmatogenous origin.

We have already said that the giant cells found in bone (osteoclasts) are phagocytic; this property, which led Metchnikoff to include giant cells amongst his group of "macrophages," is common to giant cells generally, but it is not known whether the property is universal. They englobe not only bacteria but also entire cells—indeed, a view that was at one time put forward was that the nuclei of a giant cell are the still undigested nuclei of cells that had previously been englobed and the protoplasm of which had been digested. Just as osteoclasts remove the trabeculæ of bone in rarefying osteitis, so giant cells in other parts may remove the dead fibrous tissue and fibrin resulting from inflammation. Soudakewitch in chronic inflammation of skin (*e.g.*, lupus) actually observed that giant cells surround and destroy the elastic fibres of the skin. From this it follows that giant cells may be amœboid, but whether all varieties of giant cell are amœboid, or whether they are amœboid only during certain phases of their life-history, is unknown. Neither is it known whether giant cells undergo further development, and in particular it is uncertain whether they bear a part in the formation of fibrous tissue in repair, but the balance of evidence seems to indicate that no such further development takes place. According to one view (Creighton) giant cells are vaso-formative, but there seems to be no distinct evidence in favour of this view, and there is some evidence to the contrary (Sherrington and Ballance).

VI. **The Progress of Repair.**—It will conduce to a clearer understanding of the processes intervening between the moment when an irritant commences to act and the completion of repair, if we take certain specific examples and trace them from beginning to end. For this purpose, conditions where the macroscopic appearances presented are widely dissimilar are the most suitable, for in that way the statement that the essential processes underlying inflammation and its sequels are everywhere the same will be more strikingly brought out. With this object we shall examine as shortly as possible the healing of a wound, the repair of a long bone fractured by mechanical injury, and the formation of a fibroid pleurisy.

(i.) **Healing of a Wound.**—Five methods were formerly described by which healing of a wound might possibly take place. These methods were: (i.) healing by immediate union; (ii.) healing by first intention; (iii.) healing by second intention; (iv.) healing by secondary adhesion; (v.) healing under a scab. In healing by primary union it was supposed that actual union of divided cells and fibres takes place, but there is no doubt that such a method of repair never occurs, at all events in higher animals; it may therefore be completely disregarded. The distinction made between healing by first intention and healing by second intention was, that in the former case no pus is produced, whereas in the latter case healing occurs after supervention of suppuration. Repair by second intention is the slower process of the two, and, as a rule, the resulting scar is larger than it would have been if the same wound had healed by first intention. In healing under a scab a hard mass of dried exudation, blood, etc., covers the seat of repair, but actually there is no difference in this method from the method of healing in the two previous cases. When healing under a scab takes place, however, repair is generally by first intention. Healing by secondary adhesion was said to occur when two suppurating surfaces were brought together with the subsequent formation of reparative tissue between them.

Since healing by primary union and healing under a scab must be discarded as distinctive methods of healing, we therefore reduce the methods of healing to three: (i.) healing by first intention; (ii.) healing by second intention; (iii.) healing by secondary adhesion. When these three methods have been described, it will be seen that, however different they may be macroscopically, the processes at work are in all cases the same.

The statements that have already been made in earlier parts of this chapter strongly suggest that the difference between healing by first intention (where pus is not formed) and healing by second intention (where pus is formed) depends upon the fact that microbial irritants play an important part in the latter case but an unimportant part in the former case. For pus-formation, as we have seen, is very closely bound up with the presence of bacterial irritants. This suggested difference is actually found to obtain, and we may therefore consider separately the processes occurring in an aseptic wound and those occurring in a septic wound.

(*a*) *The Wound is Aseptic. Healing by First Intention.*—If an incision be made through the living skin and subcutaneous tissues with strict antiseptic precautions, the wound gapes somewhat and the blood which escapes from the cut vessels fills the cavity. Part of this blood escapes, but part coagulates and remains between the cut edges of the wound. The knife, the tissues actually destroyed by the knife, and the blood-clot act as primary and subordinate irritants and produce inflammation in the surrounding tissues which is of small extent, but which is accompanied by the acceleration with subsequent slowing of blood-current, the migration of wandering cells, the exudation of fluid that characterise every inflammation. Around this zone of inflammation lies a zone of potential repair where there is active hyperæmia associated with exudation and proliferation of cells, principally of the connective tissue and endothelial types. These zones of inflammation and of potential repair are present in all cases; it does not matter how deep the wound may have been so long as it has involved the true skin and the patient has not died from the injury, nor how wide the edges may have gaped, nor how great an amount of clot may lie between the edges.

The exudation from the inflamed vessels and the migrated leucocytes make their way in large part to the cut surfaces of the wound and mix there with the peripheral portions of the blood-clot, forming with it a coagulum of greater or less extent, which fills the space between the cut surfaces. The coagulum rapidly contracts and brings the edges of the wound closer together, but at the same time it acts as a mild irritant and keeps up the inflammation. The tissues for a short distance from the raw surfaces therefore become œdematous from exudation and are infiltrated with wandering cells, which also invade the coagulum itself. In the coagulum, besides the contraction, there has also been going on a breaking down of the red blood-corpuscles and a setting free of irregular granules of altered blood-pigment, which, together with the *débris* of the corpuscles, is taken up by the phagocytic wandering cells and carried away, so that the coagulum, which was at first red, later becomes grey or colourless. At the same time, new formation of blood-vessels has been taking place in the zone of potential repair, and the new capillaries, lined on the outside with fibroblasts, pass into the modified coagulum, being supported by the fibrinous network as by a scaffolding. In this way the clot is vascularised by a number of young capillary blood-vessels running at right angles to the surfaces of the wound and traversing the wound from side to side. As the vessels push onwards, the fibrinous network of the coagulum, the remains of red blood-corpuscles, and probably also the finely granular oxyphil cells (which were earliest in the field), are removed by the hyaline and other phagocytic cells. Ultimately the place originally occupied by the blood-clot is occupied by a mass of young and very vascular connective tissue. Over this tissue epithelium grows from pre-existing epithelium and the space is filled up and covered over. Repair is now complete, but the young fibrous tissue contracts, obliterates in its contraction all or most of the blood-vessels, and the resulting scar becomes dead-white, and as a rule depressed beneath the general level of the skin. The length of time occupied by the process in a healthy subject depends principally upon the amount of coagulum that has to be removed and the amount of repair tissue that is required to fill the gap. If the edges of the wound, instead of being allowed to gape, are brought together, these factors are considerably reduced, the size of the resulting scar is diminished, and the actual time taken in bringing about complete repair is reduced also.

(*b*) *The Wound is Septic. Healing by Second Intention.*—In considering the healing of a wound by second intention, the chief points we must bear in mind are that the irritant (because it contains a bacterial factor) is generally more intense, that its sphere of influence is likely to spread, and, as a result of these conditions, that its action is prolonged. These facts of themselves explain why the inflammation due to the primary irritant passes into one of the pathological sequels of inflammation (pus-formation). They also indicate that the tissue destruction in this case must be greater than when the contrary conditions obtain, as they do to a large extent in healing under aseptic conditions (*i.e.*, by first intention).

Healing by second intention is a much slower process than healing by first intention. For though in both cases there is dead material to be removed before repair can be completed, in healing by first intention the irritant does not form substances which are themselves injurious to the newly proliferated tissue cells, whereas in healing by second intention the young cells are hampered in their phagocytic and reparative functions, because they are exposed to the action of highly injurious chemical substances of bacterial origin. The chronicity of healing by second intention further depends upon the fact, that a wound which is healing in this manner must heal from the bottom. This, indeed, follows indirectly from what has been already said. For where pus is being formed the tissues are degenerating, and degeneration at any spot is incompatible with repair at that same spot. It is only when the formation of pus, and with it the inflammatory changes going on in its neighbourhood have been stayed at a given spot, that the zone of potential repair lying outside the zones of inflammation and of pus-formation can become converted into a zone of actual repair.

But by the nature of the case these eventualities are matters of some difficulty. If, however, by the bactericidal action of the exudation or by phagocytosis or by any surgical intervention, the bacteria on the surface of the wound are prevented from exerting their action upon the reparative tissue, fibroblasts are able to travel further and further towards the surface of the wound, ranging themselves along the sides of newly-formed capillary blood-vessels, and ultimately the composite tissue known as granulation tissue is produced. That this granulation tissue does not break down under the influence of the bacterial poison in cases where repair takes place in the absence of special antiseptic precautions, is due to the fact that blood-plasma readily exudes and leucocytes readily migrate from the delicate vessels of which granulation tissue is so largely composed. Concerning the action of this exudation and of these cells upon bacteria we shall speak presently, but there is no doubt that but for them repair of a wound to which pyogenetic bacteria have gained access would be impossible. It is for the same reason that dangers of hæmal infection and intoxication (pyæmia, septicæmia, sapræmia) cease with the formation of granulation tissue, though no doubt the absence of lymphatics from granulation tissue plays its part also.

It is clear, then, that healing by second intention differs from healing by first intention only in the point that in the former case, the irritant being more intense and persistent, actual repair is preceded by one of the pathological sequels of inflammation. The greater degree to which irritant action enters into the process leads to a greater degree of inflammation, with its concomitant greater degrees of tissue degeneration, of exudation, of leucocytic migration. It prolongs the duration of inflammatory processes with which repair is incompatible, but since at some greater or less distance from the point of application every irritant becomes a stimulus, and since every such stimulus shows itself by proliferation of connective tissue cells and endothelial cells, the component parts of the zone of potential repair are the same in every case, whether the irritant be great or small, whether its action be prolonged or not, whether its nature be organised or unorganised. So also the changes that take place in that zone of potential repair when it becomes converted into a zone of actual repair consist in all cases, as they must of necessity consist, in new formation of blood-vessels and new formation of fibrous tissue where the epithelium is not involved, and in new formation of epithelium where the pre-existing epithelium is involved. Fundamentally there is no distinction between healing by first intention and healing by second intention.

*Healing by Secondary Adhesion.*—Healing by secondary adhesion, which is said to occur when union takes place between two granulating surfaces brought into apposition, may be dismissed very shortly. For the apposition of the two surfaces prevents the approach of fresh micro-organisms from the air, etc., and such micro-organisms as are held between the two apposed surfaces are readily dealt with by the exudation and the phagocytes. At the seat of apposition, therefore, the formerly septic surfaces are converted in a short time into aseptic surfaces and union proceeds at this spot as in a wound which has been aseptic from the first.

In all cases, therefore, repair of a wound consists in the removal of dead material and the filling up of a gap by formation of new blood-vessels from pre-existing blood-vessels, formation of new fibrous tissue from pre-existing fibrous tissue and perhaps from other sources, and formation of new epithelium from pre-existing epithelium.

(ii.) **Repair of a Fractured Long Bone.**—The second example that we shall consider, with the object of showing that inflammation and its sequels are one and the same in all situations, is repair of a long bone fractured by mechanical injury.

Here also the process may be aseptic or septic. When the fracture is "simple," *i.e.*, when there is no connection between the seat of fracture and the external air, the inflammatory and reparative processes are in most cases aseptic; when the fracture is "compound," *i.e.*, when the seat of fracture is in connection with the external air, the reparative processes at any spot are in most cases preceded by septic changes unless special precautions are taken by the surgeon and are successful.

(*a*) *Repair of a Simple Fracture of Bone* (*Aseptic*).—When a simple fracture of bone takes place, the mechanical injury which leads to fracture tears through the periosteum and endosteum in whole or in part, ruptures muscle and connective tissue with the blood-vessels that run in that tissue, and leads to effusion of blood. The effused blood collects in the neighbourhood of the fracture, both within the medullary canal and on the outside of the bone. Here it coagulates, and the coagulum gives support to the two ends of the bone and fills the space between them just as the coagulum between the edges of an incised wound fills the space between the two cut surfaces. But the coagulum also acts as a mild but persistent irritant and leads to the formation of a zone of inflammation which is surrounded by a zone of potential repair. Since the coagulum lies both within and without the shaft of the bone, the endosteum and the periosteum of both fragments are involved in the inflammatory and the potential reparative zones.

Now so far as the coagulum itself is concerned, changes take place within it identical with the changes that we have described as occurring in the coagulum between the raw surfaces of an aseptic wound. That is to say, the red blood-corpuscles disintegrate, pigment is set free, the clot becomes invaded by wandering cells, the pigment and *débris* are removed, and the clot becomes decolorised. But at the same time the proliferative changes that have been going on in the zone of potential repair, where that zone has involved the endosteum and periosteum, have led to new formation of blood-vessels and hyperactivity of the osteoblasts which are normally found in these tissues. A tissue like that of ordinary granulation tissue is therefore produced, which invades the clot, but since the cells lining the granulation loops are osteoblasts and not ordinary fibroblasts they form bone and not fibrous tissue. Hence the new blood-vessels come to lie in a matrix of young bone. The bone formed in this way is of a somewhat peculiar kind and is called "callus." It is irregular and shows none of the definite concentric rings around Haversian canals which characterise adult bone, but is rather of a spongy nature and highly vascular. The callus being formed both by the endosteum and by the periosteum, it follows that between the fractured ends of the bone, and for a longer or shorter distance within and without the upper and lower ends of its shaft, a mass of bony tissue is formed, which occupies the place originally occupied by the blood-clot. This callus has two important functions. On the one hand, it maintains the ends of the bone at rest; on the other hand, that portion which lies between the two ends (the "definitive" callus) is destined ultimately to fill up the gap and re-establish the continuity of the shaft.

In the callus further changes ensue. Just as we have seen that, in repair of a wound, the fibrous tissue formed by the fibroblasts around the granulation loops gradually increases in amount and density, leading, at the same time, to disappearance of many of the blood-vessels and of the fibroblasts themselves, so in repair of a fracture the bone formed by the osteoblasts around the young blood-vessels increases in amount and density, leading ultimately to the formation of a dense bone in which Haversian canals are more or less easily recognisable. This change is especially marked in the definitive callus. Lastly, after the definitive callus has become sufficiently firm, "provisional" callus (by which is meant all that callus which does not actually lie between the ends of the fractured bone) is no longer needed; it is therefore removed just as excess of fibrous tissue is removed after the repair of a wound is complete, and the scar is ultimately of less extent than it was at first. Removal of provisional callus takes place by a process closely akin to that which occurs in rarefying osteitis.

(*b*) *Repair of a Compound Fracture.*—It is not necessary to enter into the question of repair when the fracture is compound and septic, since the processes at work are identical with those which we have just considered, but complicated by the fact that processes discussed under the heading of caries and septic necrosis are superadded. Repair under these conditions is therefore associated with suppuration and bone destruction, and repair takes place when the irritant has ceased to act, whether that irritant be dead bone or bacteria or any other substance.

(iii.) **Formation of a Fibroid Pleurisy.**—Our third process—the formation of a fibroid pleurisy—usually commences with the occurrence of an acute or a subacute inflammation of the pleura and subpleural connective tissue, which is directly or indirectly caused by a bacterial irritant. The pleura becomes more or less hyperæmic and injected, exudation is poured out, and, whether by deposition of fibrin from the exudation or by a "fibrinoid" degeneration of the connective tissue underlying the endothelium, a false membrane is formed. Owing to the nature of the principal irritant, and the constant movement on one another of the visceral and parietal layers of the pleura, irritation is kept up, exudation is poured out in considerable quantity, and a network of fibrin ultimately fills up the space between the two layers of pleura. This fibrin holds the same position with regard to later processes that is held by the blood-clot in the two examples we have already considered; it restricts movement, and therefore lessens the degree of irritant action, it serves as a supporting structure for the young blood-vessels and the fibroblasts that are formed in the zones of repair situated on the pulmonary and on the costal sides, and possibly also it serves as nutriment for the young cells. In course of time it is removed, and between the two layers of the pleura young blood-vessels are found lying in a matrix of young connective tissue. The process, therefore, is strictly analogous to the healing of an aseptic wound, and the final result is the same, for fibrous tissue binds the two layers of the pleura together as fibrous tissue binds the two surfaces of the wound together. That separate fibrous bands (adhesions) pass from one layer of the pleura to the other in some cases, and that in others the two layers are universally adherent, is an unessential point, for in either case the final result is brought about in the same way.

In the example given above the irritant has been assumed of such a kind as does not usually lead to suppuration in this region because of its low intensity compared with the resisting powers of the tissue. Fibroid pleurisy frequently occurs when the irritant is *B. tuberculosis* or, more strictly speaking, when the irritation is produced by the tubercles themselves which result from the growth of *B. tuberculosis* in the lung. If the irritant be one of the pyogenetic micrococci (*e.g., M. pneumoniæ*) the process of repair also leads ultimately to the formation of a fibroid pleurisy. But here pus is usually produced, and, as in other cases, progress of the repair is delayed by suppuration, and repair cannot be completed until the irritant has ceased to act.

VII. **Chronic Inflammation.**—Under the name of "chronic inflammation" beside those conditions which may justly be referred to inflammation, as it has been described in the previous pages, it is common for clinicians to use the term in reference to a change which essentially consists in an increase of the interstitial connective tissue of a part. Thus when the fibrous tissue of an organ, such as the liver or kidney, is increased, they speak of "chronic hepatitis" (cirrhosis of the liver) or "chronic nephritis" (chronic granular kidney). But in these and similar cases no stage antecedent to the fibrosis can be pointed out during which inflammatory changes as such can be recognised, and though the question cannot be regarded as settled, there is growing up a tendency to separate these cases of "chronic fibrosis" from inflammation. With this view the author agrees, and, therefore, chronic fibrosis will be considered in the chapter on the pathology of nutrition.

VIII. **The Significance of Inflammation.**—Before leaving the subject of inflammation and its sequels mention must be made of the different views held with regard to the intrinsic nature of the inflammatory process. This amounts in large part to a consideration of the various definitions of inflammation that have been given from time to time.

Inflammation may be regarded from three distinct points of view: (1) from that of the established phenomena themselves; (2) from that of the means whereby the phenomena are brought into existence; (3) from that of the object which is subserved by the phenomena when they are established. These points of view may be shortly summarised in the questions: (i.) What is the essential factor in inflammation? (ii.) How is inflammation brought about? (iii.) For what purpose does inflammation arise?

Definitions of inflammation have been framed on each of these lines, in some cases taken separately, but in most cases taken two or even all three together. Now the definition given by any particular author who considers inflammation from the first point of view depends upon which of the numerous factors that go to make up "inflammation" he regards as essential, which as subordinate. The presence of an irritant, tissue degeneration, proliferation of cells, vascular dilatation, variations in rate of blood-flow, exudation of fluid, migration of leucocytes, chemiotaxis, phagocytosis, are all of them phenomena of inflammation considered in its broadest sense, and almost each single one of these has been used as a basis for a definition of inflammation. Virchow considered the tissue proliferative changes as the most important and looks on inflammation as an excessive disturbance of nutrition brought about by irritation in which the changes are principally "formative"; Rokitansky, following many of the earliest writers, believes that the vascular changes are essential; Cohnheim held that inflammation essentially consists in a molecular change in the walls of capillaries and small veins; Ziegler, that it consists in tissue degeneration combined with pathological exudation from the blood-vessels; Stricker and Grawitz, that return to an embryological condition of the cells and even of the fibres (Stricker) is the essential factor; Weigert, that the swelling is all-important; Metchnikoff, finding that phagocytosis is recognisable throughout the whole animal world when a living animal is exposed to the action of a formed irritant, looks upon phagocytosis as the fundamental principle underlying inflammation. These are perhaps the most eclectic views, and towards one or other of them approximate the opinions of many other authors. Thus Recklinghausen, Samuel, and Landerer agree in the main with Cohnheim, as indeed do most modern pathologists including Weigert. Thoma, though he wishes to discard entirely the pathological conception summed up in the word inflammation, nevertheless says that if we are to define it we can call it "a pathological disturbance characterised by exudation,"[1] and in another place[2] he describes inflammation as a "local lesion formed by the combination of the phenomena of circulatory disturbances and progressive and retrogressive tissue metamorphosis."

But even if an author have decided on his "essential" phenomenon there still remains a difficulty with regard to the means whereby that phenomenon is brought about. Even those authors who regard the vascular changes as all-important are divided amongst themselves. To explain the retardation alone in the rate of blood-flow that occurs in inflammation, there are at least Cohnheim's theory of molecular alteration in the vessel wall, the "spasmodic" nervous theory of Eisenmann, Heine, and Brücke, according to which the retardation is due to constriction of vessels at the periphery of the inflamed area, and the "attraction" theory of Vogel, Paget, and others, according to which the blood becomes thicker because the tissues exert a greater attraction than normal upon the blood-plasma. And the same is true with regard to the other phenomena.

But the difficulties already shown do not exhaust the series, for with the question, "For what purpose does inflammation arise?" there appears a totally different set of views. Fortunately, however, upon this question authors are divided into fewer separate camps, as (i.) removal of the irritant, (ii.) the production of reparative tissue, (iii.) a combination of these views, are almost the only purposes assigned. Nevertheless, there are many pathologists who strenuously maintain that inflammation is not purposeful at all. It is principally pathologists of the latter class that refuse to include repair along with inflammation, but regard them as separate processes, while those authors who include repair under inflammation are naturally those who hold the purposeful nature of inflammation.

From this chaos of views one may, however, extract the following broad statement: opinions are divided as to whether the tissue changes or the vascular changes in inflammation are in the first rank of importance and as to whether the inflammatory process itself is purposeful or not.

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[1] *Pathology and Patholog. Anat.*, trans. by Bruce, London, 1896, p. 354.

[2] *Ibid.*, p. 511.

Considering, then, the impossibility of deciding which is the fundamental process in inflammation, it is best to restrict our definition to a short description of the most characteristic points in the complex mass of phenomena which go to make up inflammation, as Thoma and Ziegler have done in the sentences given above; or else to eliminate the idea that inflammation is a state, and speak of it as a process induced by a cause, as Burdon Sanderson did long ago when he summed up the process of inflammation as "the succession of changes which occur in a living tissue when it is injured, provided that the injury is not of such a degree as at once to destroy its structure and vitality." On similar lines to those laid down by Burdon Sanderson is Adami's definition: "Inflammation is the series of changes constituting the local manifestation of the attempt at repair of actual or referred injury, or, briefly, the local attempt at repair of actual or referred injury."

Of the definitions of inflammation with which I have become acquainted those framed by Ziegler and by Adami seem the most satisfactory, but neither of them, in my opinion, is fully so. From my point of view Ziegler's definition fails (1) because it does not indicate that inflammation is purposeful (which, indeed, Ziegler does not allow); and (2) because it includes under inflammation processes which by common consent are regarded as non-inflammatory; thus in passive œdema there is "tissue degeneration accompanied by pathological exudation from the blood-vessels," and therefore this condition should, by Ziegler's definition, be inflammatory. But in cases of passive œdema inflammation is characteristically absent, except as a complication. Adami's definition, on the other hand, fails (1) because it would include under inflammation the simple regeneration of epithelium which takes place in everyday life; and (2) because it regards inflammation as an attempt at repair, whereas we have already concluded that the existence of inflammation at any spot is incompatible with repair at that spot.

**IX. Definition of Inflammation.**—In attempting to frame a definition of inflammation, I think that the following points must, *of necessity*, be borne in mind:—

1. Inflammation is a complex process and no single phenomenon can be singled out as fundamental and essential.

2. The tissue concerned in inflammation must be vascular. Inflammation is a clinical term and as such eliminates all consideration of phenomena occurring in avascular animals. On this point I side with the opponents of Metchnikoff and his school.

3. Inflammation is only one portion of the changes induced by irritant action. The conception of inflammation as a local process loses sight of the fact that parts other than that obviously affected are also involved in the results of irritant action. Upon this point little is known, but the occurrence of marked leucocytosis in some cases and of leucopenia in others, the fact that when exudation occurs in one place the tissues of the rest of the body give up a portion of their fluid to the blood, and the extraordinary effects of nerve conditions going on in other parts of the body as in Samuel's experiments (p. 289), are sufficient to show that the action of an irritant really extends far beyond the regions of its obvious action. It does not seem just to speak of inflammation as a reaction of tissues to an irritant, and to restrict that reaction to the parts alone where it is obvious. One is not justified in speaking of the hyperæmia and the exudation as "inflammatory" and in neglecting entirely the compensatory anæmia and drying of the tissues to which they must give rise in other parts. Even if "inflammation" be restricted to the local manifestations it must be made clear that it is only a portion of the total results of irritant action.

4. The degenerative changes induced by the irritant are no part of inflammation. But for this exclusion an eschar or a slough would be inflamed tissue, and this it cannot be, for inflammation only occurs in living tissues. The degenerative changes are causes and results of inflammation, but not parts thereof.

5. Proliferative changes, being induced by stimuli and not

by irritants, are to be severed entirely from inflammation; hence repair is independent of inflammation.

6. Inflammation is directed towards an end. Its object is to neutralise the irritant action, to limit its effects, and to supply an additional amount of nutriment to those tissues whose vitality has been lowered but not extinguished. The force of this statement is not invalidated by the argument that inflammation is sometimes followed by injurious results any more than the statement, that gastric digestion is directed towards an end, is invalidated by the argument that in some cases perforation of the wall of the stomach occurs during digestion.

7. Inflammation is not a reparative process, for inflammation at any spot is incompatible with repair at that spot. Inflammation is only preparatory to the onset of repair when repair occurs under certain conditions.

Bearing these points in mind I would venture to define inflammation as follows:—Inflammation is the local portion of that preparation for local repair which is called forth in the living animal body by the action of an objective or subjective irritant upon a vascular part.

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# CHAPTER IX.

## THE PATHOLOGY OF INFECTION.

*Synopsis.*

- I. Infection.
  - (i) The Infective Agent.
  - (ii) Incubation.
  - (iii) Contagion or Direct Infection.
  - (iv) Indirect Infection.
- II. Types of Infective Disease.
  - (i) Intoxicative.
  - (ii) Septicæmic (Bacteriæmic).
  - (iii) Change of Type of Infective Disease.
  - (iv) Variation of Type in Different Animals.
- III. Personal Factors influencing the Occurrence of Infection. Susceptibility and Immunity.
  - (i) General.
  - (ii) Susceptibility.
    - A. Natural.
    - B. Acquired.
  - (iii) Immunity.
    - A. Natural.
    - B. Acquired—
      - (*a*) Active.
      - (*b*) Passive.
    - C. Inherited Susceptibility and Immunity.
  - (iv) Local Immunity.
- IV. Bacterial Factors influencing the Occurrence of Infection.
  - (i) Dose.
  - (ii) Seat of Inoculation.
  - (iii) Virulence.
  - (iv) Presence or Absence of Toxin.
  - (v) Symbiosis.
- V. Certain Properties of Blood-Serum.
  - (i) Bactericidal.
  - (ii) Antitoxic.
  - (iii) Pfeiffer's Phenomenon.
- VI. Theories of Immunity.
  - (i) The Exhaustion Theory.
  - (ii) The Retention Theory.
  - (iii) The Phagocytic Theory.
  - (iv) The Humoral Theory.
  - (v) The Cellulo - Humoral Theory.
    - Specificity of Immunity. Method whereby Anti-Substances produce Immunity.
- VII. Latency in Infective Disease.
- VIII. Relapses.

IN the preceding chapters reference has frequently been made to the part played by bacteria in the causation of disease, and incidentally certain diseases which are caused by bacteria have been spoken of as "infective." Now the "infective" diseases form a group which was clinically separated long before their connection with bacteria was suspected, and the essential point which led to their separation was that the diseases in question are communicable either directly or indirectly from animal to animal. Communicability of the disease was therefore taken as the characteristic feature of the infective diseases. We now know that when bacteria are the causes of disease, these diseases are, within limits, communicable from animal to animal, and therefore the infective diseases of the clinician come to be in large part co-terminous with the bacterial diseases of the pathologist. But not entirely. For though we have reason to believe that infective diseases are due to bacteria in all cases, strict proof is wanting in such eminently infective diseases as syphilis, scarlatina, etc., owing to the fact that specific infective agents have not as yet been certainly demonstrated in these diseases. In another direction the pathologist's view of infective disease is wider than that of the clinician; for the pathologist, tetanus is an infective disease, but, at all events until recently, it would not have been so regarded by the clinician, communication of tetanus from animal to animal, excepting in the way of a laboratory experiment, probably being quite unknown.

But even though a disease may be communicable from animal to animal, and even though the *causa causans* may have been isolated, it does not follow that infection takes place whenever an animal not suffering from the disease is brought into relation with an animal suffering from the disease. Though communicable, the disease in such a case is not communicated. The failure of infection may depend upon some peculiarity which concerns the micro-organism itself, such as its nature, or its virulence, or the dose in which it is inoculated, or may depend upon some peculiarity of the animal exposed to infection. When the peculiarity resides in the animal, we have to deal with conditions summed up in the terms "insusceptibility," "resistance," "immunity." On the other hand, where infection does occur, this may also depend either upon some peculiarity which concerns the micro-organism or upon some peculiarity which concerns the animal exposed to infection. When the peculiarity leading to infection resides in the animal, we have to deal with conditions summed up in the terms "susceptibility" and "predisposition."

These subjects of infection, immunity and susceptibility, will now be discussed, and along with them the pathology of "relapses" and "latency" of infective disease. Owing to the youth of bacteriology as a branch of pathology, the subjects are at present very obscure in many points, and a general indication of the trend of opinion at the present day is all that must be expected.

I. **Infection.**—(i.) **The Infective Agent.**—Of all conditions necessary for infection a power on the part of the infective agent to carry on a parasitic existence—whether obligatory or facultative — is the most important. It is true that a saprophyte, such as *Aspergillus niger*, may cause disease, and that, in sapræmia, saprophytes produce the toxic substances which, by their absorption, lead to clinical symptoms, but in neither case have we to deal with an infective disease, because exceptional conditions on the part of the patient must coexist with the presence of the micro-organism. Theoretically, conditions can exist under which any micro-organism may be the cause of disease, just as, theoretically, any micro-organism may lead to pus-formation. But practically, just as certain parasitic micro-organisms are distinguished as being especially associated with pus-formation in that they lead to suppuration without the coexistence of extraordinary conditions on the part of the animal, so certain parasitic micro-organisms are distinguished as being especially associated with infective disease in that no exceptional conditions are necessary on the part of the animal for the production of disease by these micro-organisms. An infective disease, therefore, is one which is produced by the entry into and the multiplication within the body of a normal animal, from without, of an obligatory or a facultative parasitic micro-organism.

(ii.) **Incubation.**—In the production of disease the chief action of a pathogenetic micro-organism is not mechanical,[1] but as has already been said a toxin is produced, and to the action of that toxin the lesions which go to make up the disease are mainly due. Every infective disease, therefore, becomes essentially an intoxication with chemical substances, but the difference between them and sapræmia is, that in sapræmia the laboratory for the formation of toxin is physiologically outside the body, whereas in the infective diseases the laboratory for toxin-formation is physiologically within the body.

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[1] Reference is, of course, made only to vegetable micro-organisms.

Now since the symptoms of any given infective disease are due to the action of a specific toxin on the animal, it follows that those symptoms cannot manifest themselves, even though the specific micro-organism be actually present in the animal, until the minimal amount of toxin necessary for the production of symptoms is also present in the animal. In some cases, no doubt, this amount of toxin may be introduced at the moment of inoculation with the micro-organism, or even—as in the cases of experimental diphtheria and tetanus—the symptoms of the disease may be produced by introduction of the toxin alone. But such cases are artificial, and are hardly to be seen outside the laboratory. In the vast majority of cases, the amount of toxin actually introduced at the moment of infection is negligible, and the toxin which ultimately leads to the appearance of symptoms is formed by the micro-organisms after their entry into the body. For this production of toxin a greater or less length of time is necessary, during which the micro-organism multiplies and forms toxin, it is true, but during which symptoms of the specific disease are absent, and possibly the patient may appear to be in perfect health. The period which elapses between the inoculation and the appearance of the first specific symptoms of the disease is called the "period of incubation," and the existence of an incubation period of variable length is characteristic of the infective diseases.

Each specific infective disease has its own particular incubation period, but the length of incubation of any given infective disease is somewhat variable. Since the rate at which the micro-organism grows and produces toxin depends upon a variety of circumstances, variability in length of incubation period is hardly to be wondered at; cause for wonder is rather given by the comparative constancy of the lengths of incubation of different infective diseases.

(iii.) **Contagion, or Direct Infection.**—A clinical subdivision of the infective diseases is found in the group known as the "contagious diseases." Strictly speaking, a contagious disease is one in which communication of the disease to a healthy person can only occur if that healthy person come actually in contact with a person suffering from the disease; but practically a disease is called "contagious," though infection is carried by an intermediate person or object, if the length of time during which the infective material is upon the intermediary is very short. Bacteriologically the essential condition is that the infective agent cannot maintain an existence and multiply outside the animal body, and hence contagious diseases, strictly speaking, can only be caused by obligatory parasites. Latterly, "contagion" has to a large extent been used loosely as synonymous with "infection," but, as has just been said, it can only be regarded as a subdivision of infection.

Contagion may be immediate or mediate, but examples of disease in which immediate contagion alone occurs must be very rare, if any really exist. For not only in such a case must the micro-organism be an obligatory parasite, but also it must of necessity perish immediately on its removal from its host. Contagion in the broader sense, as including mediate contagion, is a well-known condition, and several contagious diseases are recognised. Syphilis may serve as an example of diseases in which a close approach to strict immediate contagion is observed. In the vast majority of cases the disease is contracted from a person at the time suffering from syphilis, through an abrasion of a mucous membrane or the skin. But mediate contagion can also occur. Cases are known in which a woman not herself affected has nevertheless carried the disease to others, as, for example, when a previously healthy man has become infected after sexual intercourse with a woman immediately after intercourse between her and a syphilitic man had taken place. Even more definite evidence of mediate contagion is given by those undoubted cases in which a syphilitic sore has appeared on the chin at the seat of a slight cut inflicted during shaving, when the razor has previously been used by a syphilitic person and has in some way been contaminated by him, or by the cases in which a syphilitic sore appears on the lip or tongue of a previously healthy person after he has smoked the pipe of a subject of secondary syphilis. Under no circumstances, however, have we reason to suspect that the syphilitic virus multiplies on a carrier of contagion, or in other words, that it is capable of a saprophytic existence.

(iv.) **Indirect Infection.**—Many examples are known of diseases that are indirectly infectious: anthrax, typhoid fever, cholera, tuberculosis, diphtheria, and many others. Bacteriologically the infective agent in these cases must be a facultative saprophyte. In not a small number of cases of this kind, however, the disease is *actually* communicated by contagion, immediate or mediate, for it is obvious that though a contagious disease cannot possibly be communicated by indirect infection, an indirectly infectious disease may be and is readily communicated by contagion. Quite apart from laboratory experiment in which mediate contagion is a very common procedure, it is certain that many cases of diphtheria, for example, in the human subject are due to contagion, immediate or mediate, and the same is probably true in some cases of typhoid fever.

The ease with which indirect infection can occur necessarily depends upon the ease with which a pathogenetic micro-organism can carry on a saprophytic existence. Typhoid bacilli and the vibriones of Asiatic cholera can live and multiply in water in which only a trace of albuminous material is present; diphtheria bacilli and the, as yet, unrecognised micro-organism of scarlatina[1] can live, and certainly, in the case of diphtheria bacilli, can multiply, in milk; so that these diseases can be conveyed to a great distance, and from one case disease may be communicated to a large number of individuals. With regard to cholera and malaria—the last-mentioned disease being due to an animal parasite, it may, of course, be subject to somewhat different laws —many medical practitioners, in localities where these diseases are endemic, consider that air is an important carrier of infection, but the general tendency among bacteriologists is to deny that any great part is played by air in this way, at all events with regard to these diseases. On the other hand, where the infective agent forms spores, which can maintain existence for an unlimited time in a dry condition, the importance of transport by air is fully recognised by bacteriologists. The fact, to which reference has already been made, that at least actinomyces, tubercle, and diphtheria are capable of existing in a mycelial as well as in a bacillary form is of great importance; it clearly indicates that the saprophytic existence which is known to obtain for actinomyces may also be normal, or at least is possible for the other two micro-organisms.

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[1] In his work on *Micro-organisms and Disease*, pp. 149 and 151, Klein describes a "*Streptococcus scarlatinæ.*"

II. **Types of Infective Disease.**—Though all infective diseases are alike in that the toxins elaborated by bacteria are the real causes of the symptoms presented, there is no doubt that infective diseases are of different types.

(i.) In some cases the pathogenetic bacteria grow and multiply locally and do not gain access to the blood or tissues, at all events in sufficient numbers for recognition by means at our disposal. Of this class is tetanus, and if we put on one side the rare cases in which bacilli have been found in internal organs, diphtheria is an example also.

(ii.) In other cases the pathogenetic bacteria gain access to the blood-stream and are found in the tissues, forming their toxic substances directly in the blood and tissues. Of this class are all those diseases in which hæmal infection or bacteriological "septicæmia" occur. Theoretically the difference between the two classes is of extreme importance, for in the first class local treatment of the seat of infection, if undertaken before there has been a sufficient multiplication of the bacteria and manufacture of toxin, should cut short the disease, just as in sapræmia removal of the putrefying mass cuts short the disease. On the other hand, when one has to deal with the second class of infection, no local treatment has the least chance of success; the bacteria are in the blood and tissues, and it is in the blood and tissues that they must be attacked.

(iii.) The type of an infective disease may change. It has already been pointed out that a disease at first local may afterwards become general, and in the case of all hæmal infections a primary local focus has no doubt existed, though possibly it may have been overlooked. Leaving on one side all considerations of virulence, dose, seat of inoculation, etc., the question whether the action of a given infective agent remains local, or whether it becomes generalised, seems to depend upon the relative susceptibility or insusceptibility of the individual into which the inoculation takes place. Thus, anthrax, which in the mouse or guinea-pig becomes generalised so that even the capillaries are densely crowded with bacilli at the time of death, in man leads to a localised pustule and becomes generalised only in rare cases. Here we have differences in type of infective disease due to racial difference in susceptibility of the infected species of animal; to make the series complete it may be added that in the normal frog inoculation of anthrax bacilli leads to no disease whatever. The same series of phenomena may be observed in one and the same species of animal when resistance to the disease has been artificially raised or lowered in different individuals thereof. Thus in a normal guinea-pig subcutaneous injection of diphtheria bacilli leads to a local swelling followed by death in 24–48 hours, but bacilli are absent from the blood and organs; if a guinea-pig whose resistance has been lowered be inoculated, local swelling and death occur as before, but bacilli may be found in the tissues or blood. If, on the other hand, the animal's resistance has been slightly increased, instead of a local swelling and death, a local necrosis of tissue with illness of the animal may occur, but ultimately the animal will recover; if the resistance has been still more increased necrosis will be absent and the animal will only be slightly indisposed for a short time; while, if the resistance has been raised to a very high degree, local subcutaneous injection of diphtheria bacilli may practically be followed by no result at all.

(iv.) The type of infective disease is not the same in all animals. This point is very important. We know that in the human subject typhoid bacilli are associated with a certain disease known as typhoid fever, and we recognise that disease by the changes found in the Peyer's patches in the small intestine, by the cutaneous eruption, by the swelling of the spleen, and so on. We know further that if typhoid bacilli, obtained from a case of typhoid fever in man, be injected into such an animal as the guinea-pig, it produces a disease which is probably followed by death. But the disease in the guinea-pig is not typhoid fever as we know it in man. The spleen, indeed, may be swollen and there may be diarrhœa, as in human typhoid fever, but cutaneous eruption, and intestinal lesions in particular, are absent. The same is true of Asiatic cholera. Cultivations of vibriones obtained from cases of human Asiatic cholera, when injected into guinea-pigs, may produce death, and the animal may die in a collapsed condition as does the human patient, but the symptom-complex of cholera, and in particular the "rice-water" stools, are not commonly seen, though they are said to occur under certain special conditions.

In the case of diphtheria, on the other hand, resemblance between the effects of artificial inoculation of guinea-pigs and the human disease is commonly much greater. If the vaginal mucous membrane of young guinea-pigs be inoculated with diphtheria bacilli, a pseudo-membrane similar to that which normally occurs in the throat, but which may appear on the vulva of human patients, is produced. A further and most important point of resemblance lies in the fact that paralyses may occur in both lower animals and man. In tetanus the resemblance is even more striking, for the similarity between the tetanic spasms of man and of the lower animals when both are the subjects of tetanus is well-marked. Though we are not here dealing with an infective disease, it may be mentioned that the greatest similarity in the effects of inoculation are seen when a poison such as cobra-venom is injected, for the train of symptoms in lower animals and in man are identical.

It will be noticed that those cases in which the similarity between the effects produced in man and in the lower animals is greatest are precisely those in which toxic action is best marked. In typhoid fever and in cholera, formation of a toxin by the micro-organisms usually considered to be associated with those diseases is much more doubtful. Indeed, according to some authors the symptoms of typhoid fever and of cholera are due to toxins prepared in the intestines by micro-organisms other than the typhoid bacilli and the cholera vibriones, and absorbed into the body through an intestinal wall whose normal inhibitory power against absorption of toxins has been impaired by the action of the typhoid and the cholera microbes respectively. Further research is necessary before these latter points can be decided, but the facts mentioned indicate that arguments derived from experiment on animals must only be applied to the human subject after careful consideration.

The type of an infective disease is therefore not a constant factor of the specific micro-organism alone, but is modified by factors which concern the individual in which the micro-organism is inoculated. Nevertheless, as we shall see later, the characters of the micro-organism itself have important bearings upon the effects which follow its injection into an animal.

III. **Personal Factors influencing the Occurrence of Infection: Susceptibility and Immunity.**—(i.) **General Considerations.**—In commencing the study of these subjects certain general statements must be made at the outset: (*a*) Susceptibility and immunity are relative and not absolute terms. So far as is known, no animal is insusceptible to a particular disease under all circumstances, though in some cases the insusceptibility is so great that extraordinary measures have to be adopted before it is broken down. When, therefore, it is said that an animal is susceptible or immune to a certain disease, it must be understood that these attributes do not imply that under all conditions or under no conditions, respectively, does the animal become infected with the disease, but rather that a minute dose is sufficient or an enormous dose is necessary, as the case may be, for the production of the particular disease in the particular animal.

(*b*) A given infective agent is not equally pathogenetic to all animals, in other words, the susceptibility of different species of animal to a given pathogenetic micro-organism is a variable. Examples of this fact have already been given above. The following are also cases in point. The dog, goat, ass are so resistant to the *B. tuberculosis* that they may be said to be immune—on the other hand, the guinea-pig is extremely susceptible to the same micro-organism. So also the guinea-pig is highly susceptible to diphtheria, but the mouse is practically insusceptible. Similar differences may even be observed between varieties of one species. Thus Algerian sheep are immune to anthrax, other varieties of sheep are susceptible; the field mouse is highly susceptible to glanders, the white mouse is practically immune; the negro is relatively insusceptible to yellow fever, whites are highly susceptible. Examples of both these classes of case might easily be multiplied.

(*c*) The degree of susceptibility to or immunity from infective disease may become altered either in the direction of increase or in that of decrease. This may be brought about either by natural or by artificial means, the importance of which is so great that they will call for special consideration.

(ii.) **Susceptibility or Predisposition.**—An animal may be naturally susceptible to a given disease (when that property may be peculiar to its race or to itself), or its susceptibility may have been acquired directly or may have been transmitted to it by its parents. We therefore differentiate

A. Natural Susceptibility or Predisposition.
B. Acquired Susceptibility or Predisposition.
C. Inherited Susceptibility or Predisposition.

A. **Natural Susceptibility.**—This condition is said to exist only when susceptibility is great and when the animal may otherwise be regarded as normal. In the case of the mouse and anthrax, susceptibility is so great that, if an animal be inoculated with anthrax at the tip of the tail and the lower portion of the tail be amputated, even within one minute, the animal will die of anthrax. The natural susceptibility of man to syphilis is also very great; excision of the seat of infection, however short a time after infection, has probably never been followed by freedom from subsequent development of the disease. Certain individuals show a marked natural susceptibility to infective disease of all kinds; thus, in a case personally known to the author, a healthy woman of 27 years had suffered from small-pox, scarlatina (twice), measles, whooping-cough, influenza (five separate attacks), and diphtheria, besides innumerable attacks of follicular tonsillitis and catarrh; her brother, whose occupation was closely similar, during the same number of years only contracted measles, whooping-cough, influenza (a mild attack), and catarrhs. Where natural susceptibility is small, it comes practically to the existence of a relatively high degree of natural immunity.

B. **Acquired Susceptibility.**—Here we have to deal with individual peculiarity alone as distinguished from that of races or of varieties. A susceptibility may be acquired, or a natural insusceptibility may be broken down by a variety of conditions, of which the following are the chief:—

(*a*) *Age.*—Susceptibility to infective disease of all kinds is greater in youth. In the human subject the frequency with which such infective diseases as measles, mumps, scarlatina, whooping-cough affect children is a matter of common knowledge. Newly-born infants seem to be an exception to this rule, for in them susceptibility to infective diseases of most kinds is less than it is between the second year of life and puberty; this immunity may in part depend upon a smaller exposure to infection, but probably also depends upon their absorption of immunising substances with the mother's milk. A good example of the effect of age is given by the white rat in the case of anthrax, for though the adult white rat is insusceptible to anthrax the young white rat is very susceptible.

In advanced age susceptibility does not seem to be greater than in adult life, but at least in human beings this may be because, by the time old age has been reached, an acquired immunity has been obtained to the diseases to which the individual is most liable to be exposed. The resisting power of the organism to disease generally in old age as in extreme youth is less than it is in adult life, but I have been unable to find evidence upon the special question of susceptibility to *infective* disease in old age.

(*b*) *Hunger and Thirst.*—Canalis and Morpurgo showed that, by starvation, pigeons, which are normally resistant to anthrax, are rendered very susceptible. To be effective, these authors found that starvation must be continued after inoculation; if the birds are starved before, but fed after, inoculation, they survive, unless the hunger period has been greater than six days. Pernice and Alessi proved that dogs, hens, pigeons, and frogs can be rendered susceptible to anthrax by depriving them of water.

(*c*) *Improper Food.*—Hankin showed that the refractory white rat may be rendered susceptible to anthrax by feeding upon sour milk and bread. In the same way it has been found that the presence of sugar in the blood, as when phloridzin is administered, increases susceptibility of the animal in some cases.

(*d*) *Exposure to Heat, Cold, and Moisture.*—Several examples of the effects of these agents are known. Two of the most striking are, that on immersing a hen in cold water she loses her resistance to anthrax (Pasteur), and that a frog, if kept at a temperature of 25°–35° C., succumbs to inoculation with anthrax (Petruschky).

(*e*) *Fatigue and Loss of Blood.*—Charrin and Roger have shown that the natural immunity of the white rat is broken down by causing the animal to work in a rotating cage until thoroughly fatigued. Rodet produced an acquired susceptibility in animals by inducing general anæmia from loss of blood.

(*f*) *Removal of Organs.*—Several experimenters have found that after removal of important organs, especially the pancreas (Canalis and Morpurgo) and the spleen (Tizzoni and Cattani), susceptibility to infective disease is increased. It was at first thought that these experiments prove the organs in question to have some special connection with natural immunity. But greater care in experiment and re-establishment of the animal's health before inoculation have shown that the acquired susceptibility is not due to absence of the function of any especial organ, but simply to the shock, etc., which necessarily follows a serious operation.

In the human subject we have of course no evidence comparable with that obtained on lower animals, but it is a well-known fact that insanitary conditions, exposure, bad and insufficient food, mental worry and physical fatigue, all of which are included under the general term "depressing conditions," are associated very closely with tuberculosis. The lower death-rate from infective disease generally, and from tuberculosis in particular, which has been observable in England during the past twenty years or so, must be associated with the better personal and public hygiene and the improved standard of living that have existed over the same period. The increased susceptibility of patients to infective disease after severe operations is highly important from a surgical point of view.

C. **Inherited Susceptibility.**—This branch of the subject will be postponed until it can be discussed along with inherited immunity.

(iii.) As with susceptibility so with immunity we have to distinguish three varieties :—

A. Natural immunity.
B. Acquired immunity.
C. Inherited immunity.

A. **Natural Immunity.**—This form of immunity may be seen in species, in varieties, or in individuals, but enough has already been said upon the point in Section III. (i.) (*b*) of this chapter (p. 382).

B. **Acquired Immunity.**—Of this variety of immunity there are two distinct kinds, which have been distinguished as "active" and "passive." These are so different that they must be treated separately.

(*a*) *Active Immunity.*—An active immunity may be acquired in five different ways at least.

*a.* The natural susceptibility to a given infective disease may be removed after recovery from an attack of that disease. Examples of this method are very common in ordinary life; the person who has suffered from such diseases as measles, scarlatina, mumps, or whooping-cough probably never has another attack of the same disease during the remainder of his life. Here the acquired immunity is permanent, but in other cases immunity may be of shorter or even of very short duration. Thus for a short time after recovery from an ordinary catarrh the patient is immunised, but within a few weeks or months the immunity disappears. With erysipelas, cholera, and influenza the immunity conferred by an attack of one of these diseases is so short that it may almost be said to be non-existent, indeed many surgeons have maintained that one attack of erysipelas actually predisposes the patient to a second.

$\beta$. Immunity may be acquired by inoculation with attenuated micro-organisms. The best example of this mode of procuring immunity is probably afforded by vaccination, though we are still ignorant of the bacteria concerned, unless the results of Klein and of Copeman are fully accepted. It is generally allowed that vaccinia is variola or small-pox attenuated by passage of the disease through the cow; we may therefore regard vaccination as inoculation with an attenuated form of that disease against which we wish to confer an immunity. Intentional inoculation with small-pox as it was practised in the eighteenth century was an example rather of the first than of the second method, for though the variolous matter was taken from mild cases it could not be said to be attenuated, since it not infrequently produced severe—even fatal—disease in the inoculated persons. Pasteur applied the principle of inoculation with attenuated virus to chicken-cholera, anthrax, and other diseases with greater or less degrees of success. Haffkine's method of anti-choleraic inoculations practically belongs to this class.

$\gamma$. Immunity may be conferred by inoculation with small doses of virulent micro-organisms.[1] In this method it is obvious that a direct attempt is made to copy nature. The dose inoculated must of course be less than the minimal lethal dose. When the animal has recovered, it is found to possess a certain degree of immunity, and one is able, by gradually raising the dose of virus injected in successive inoculations of the same animal, to raise the degree of immunity which it possesses. Ultimately the animal may withstand with ease a dose equal to many times the dose which would at first have been fatal.

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[1] Klein (*Centralbl. f. Bakt.*, etc., vol. xx., 1896, p. 417) produced an immunity to diphtheria in guinea-pigs by successive injection into the peritoneal cavity of large quantities of living diphtheria bacilli taken from cultures on gelatine. The guinea-pig is much less susceptible to intra-peritoneal than to subcutaneous inoculation with diphtheria bacilli. Reference will be made to this experiment later.

δ. The most important method we possess for obtaining acquired immunity is that introduced by Salmon and Smith in America. These investigators found that, if the sterilised products of the bacillus of hog-cholera be injected into pigeons, the birds become resistant to subsequent inoculations with the bacillus itself. This method is of vast importance, both from a practical and from a theoretical point of view. The theoretical side of the question will be left for the present, but from a practical point of view the discovery is important, because it permits of better regulation of the dose used for inoculation. In laboratory experiments, except for special purposes, this method has superseded the others. Numerous examples of immunity acquired in this manner are known, but the most striking are perhaps those obtained in the cases of *B. tetani*, *B. diphtheriæ*, and *B. pyocyaneus.*

Just as, when conferring immunity by doses of virulent micro-organisms, it is necessary to commence with doses far below the lethal dose, and to gradually increase the amount inoculated, so in this method of "immunisation by chemical products" it is necessary to begin with very small doses of the toxin and to gradually increase the dose as immunity is being acquired. If this process be carried out with care, an animal may in time acquire so great a degree of immunity that it will withstand an injection of many hundred times the dose of poison that would have, at first, killed it with certainty. This method is adopted (in some cases in conjunction with inoculation of cultures of living and virulent bacilli) in the preparation of anti-diphtheritic serum from horses. There is a limit, apparently, for each animal, beyond which an acquired immunity of this kind cannot be pushed, but excepting the bare fact nothing is known at present upon this point.

ε. It has been found that an immunity may be acquired after feeding an animal with toxin. Little is known with reference to this method, but it is of great interest in connection with the beneficial results obtained in myxœdema by feeding with thyroids of the sheep.

(*b*) *Passive Immunity.*—It was found by many observers, amongst whom Behring stands pre-eminent, that when an animal has, by any of the methods described above, been immunised against a given infective agent, the blood-serum of that animal, if inoculated into other animals, can confer upon them also an immunity against the same infective agent. This statement may be regarded as a general law. Since the second animal in this case has not been "actively" immunised by the specific micro-organism or its toxin, but is simply made to share in the immunity which inoculation of the specific micro-organism or its toxin has produced in the first animal, this method of immunisation has been distinguished as "passive."

The truth of the law given above is now firmly established; it has been demonstrated in the cases of rabies, of tetanus, of diphtheria, of pneumonia, and of other diseases. Ehrlich extended the range over which this law holds good by showing that animals may be actively immunised against ricin (the active principle of castor-oil beans) and abrin (the active principle of jequirity seeds), and that the blood-serum of such immune animals is able to confer passive immunity against ricin and abrin respectively in other animals. And Calmette, whose work has been confirmed by Fraser, has recently shown that the same holds good with reference to animals immunised by successive small doses against snake-venom.[1]

The importance of this method of conferring immunity lies in the fact that it is not only protective, but also is curative. Not only by a previous injection of serum from an immunised animal can a subsequent inoculation with the poison (or, in the case of bacterial poisons, with the bacteria) be rendered abortive, but also if a sufficiently large injection of the serum be given after symptoms of the disease have appeared, those symptoms are cut short, and the patient recovers. The amount of the specific serum necessary for *cure* is, however, greater than the amount necessary for *prevention*, and the probability of cure varies inversely with the length of time after inoculation with the micro-organism that elapses before injection of the serum is carried out.

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[1] In spite of many attempts an immunising serum has never been prepared for alkaloidal poisons such as morphia and strychnia.

Passive and active immunity show important differences. In particular, passive immunity appears very rapidly after injection of the immunising serum, active immunity, on the other hand, does not appear for days, or even weeks, after inoculation with the toxin or bacteria; passive immunity varies with the immunity of the animal whence the serum was obtained and the amount of serum injected, active immunity is only within limits proportional to the amount or intensity of the virus (toxin or bacteria) used for injection; passive immunity is only temporary, active immunity is (relatively) permanent.

C. **Inherited Susceptibility and Immunity.**—Though little is known concerning other forms of immunity and susceptibility, still less is known concerning hereditary transmission of these characteristics. But the fact among others that the children of tubercular parents are very liable to suffer from tuberculosis shows the importance of the question.

Now, when the child of tubercular parents itself suffers from tuberculosis, it may either be born with evidence of the disease, in which case the tuberculosis is "congenital," or the disease may not be developed till later in life, perhaps in the first or second year, perhaps in early adolescence.

Where the disease is congenital, infection must have been derived either from the father through the semen or from the mother. With regard to paternal infection, though it is certain that the semen of tubercular persons may contain tubercle bacilli, the occurrence of direct infection of the ovule is very doubtful; probably in all cases of congenital tuberculosis the mother herself has been infected first.[1] With regard to maternal infection it is known that the mother may directly infect her offspring *in utero* with typhoid fever, with small-pox, with malaria, and in these cases the micro-organisms concerned must have passed through the walls of the maternal and fœtal blood-vessels in the placenta; nevertheless it is doubtful whether such passage of micro-organisms can take place when the placenta is healthy. For congenital tuberculosis we may therefore regard an antecedent maternal infection as being most probable.

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[1] According to Kanthack (Allbutt's *System of Medicine*) this may be said of all infective diseases with the bacteriology of which we are acquainted. In syphilis, direct paternal infection may *apparently* take place in that a syphilitic child may be born without any evidence of the disease being presented by the mother; but that her tissues are modified in some way is shown by the fact that though such a child will infect a wet nurse it will not infect its own mother.

But when disease is contracted in later life at least three explanations are possible: (1) Infection may take place because of the existence around the child of an atmosphere more highly charged with tubercle bacilli than normal, *i.e.*, the risk of infection is abnormally great. There can be no doubt that such increased risk obtains in cases where the tubercular parent or parents are still living and the subjects of active tuberculosis of the lungs. The number of bacilli expectorated with the sputum is frequently enormous, and the carelessness of tubercular patients with regard to disinfection of their sputum, combined with the great vitality shown by tubercle bacilli where drying is concerned, must lead to the suspension in the air of large numbers of potentially active bacilli. Even in hospitals for consumption, where great care is taken to disinfect expectoration, the air contains relatively large numbers of tubercle bacilli. (2) The child may possibly inherit a susceptibility which exists in its parents as shown by the occurrence of tuberculosis in them. This condition is the only one which could strictly be called "inheritance of susceptibility," and it has long been held that such an inheritance is the chief cause of the appearance of tuberculosis in the children of tubercular parents. If the inheritance of parental characteristics, physical as well as mental, is borne in mind, the possibility of such an explanation cannot be denied, but its actual existence is extremely difficult of proof. In some cases a special individual susceptibility is recognised, as for example where one member of a family, in which for three generations no case of tuberculosis has ever been known, suddenly contracts the disease and dies in a few weeks or months of "galloping consumption." On the other hand, a special individual immunity is sometimes seen, as where a father, mother, and seven brothers and sisters have died from tuberculosis but yet one member of the family (aged 50), in spite of having lived for eighteen years in a hospital for consumption, has nevertheless remained perfectly well.[1] (3) The bacilli may have been introduced during fœtal life but have remained "latent." To this point reference will be made later.

Turning now to the subject of inherited immunity. Immunity of the young of immunised parents to anthrax, to rabies, to tetanus, and to *B. pyocyaneus*, has been experimentally recognised, and reference has already been made to the fact that newly-born infants show a marked immunity to diseases to which in later life they become susceptible. Here again at least three explanations are possible: (1) The child may partake of an acquired immunity possessed by its mother. In this case the child would be the subject of a passive immunity, differing only from passive immunity as we know it in other cases by the particular method in which the protective serum is introduced from one individual into another. The fact that the immunity present in the newly-born gives place to a susceptibility within a few weeks or months of birth completes the analogy with other cases of passive immunity. (2) The child may have itself acquired an active immunity, though *in utero*, from having itself passed through an attack of the disease, or from having received repeated doses of toxin through the blood-plasma of the mother. Under either of these two conditions the mother must have been suffering from the disease during her pregnancy. (3) An immunity present in the father or mother may have been transmitted directly to the embryo.

Strictly speaking, the last of these possibilities alone should be called "inheritance of immunity," but there is reason to believe that in a large number of cases—perhaps the majority—of "inherited immunity" the young is immunised by either the first or the second method. In the case of *B. pyocyaneus*, Charrin and Gley have done some important work in an endeavour to investigate inheritance of immunity in its strictest sense. Male rabbits (the rabbit may be said to possess no natural immunity whatever to *B. pyocyaneus*) were immunised by repeated subcutaneous injections of pyocyaneus *toxin*. Fifteen to eighteen days after the last injection, by which time previous experience had shown that no toxin is present in the animals, each of the males was placed in a cage with a normal healthy female. Of thirty-six young born alive from these parents, Charrin and Gley found that three possessed a greater or less degree of resistance to inoculation with the *Bacillus pyocyaneus*, though the mothers themselves were still highly susceptible in all cases but one. Though rare, a strict inheritance of immunity may therefore be allowed to exist. When both parents had been immunised the percentage was much higher, eight young out of twenty-three showing resistance to inoculation with the disease.

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[1] The examples given have come under the author's personal observation; the family history of the last case is a curious combination of the opposite conditions under discussion.

(iv.) **Local Immunity.**—In all the forms of immunity that have hitherto been considered the condition has been one appertaining to the body as a whole, and for that reason they may be summed up under the term "general immunity." But Cobbett and Melsome have found that besides a *general* immunity we may also have a *local* immunity. Upon this point we have as yet little information, but the authors mentioned have found that the result of inoculating the rabbit's ear with *Strept. erysipelatis* differs according as the ear has or has not been the seat of a previous recent attack of erysipelas. In the normal ear, inoculation is followed by an inflammation which usually commences not earlier than the third day, which is at its height about the seventh or eighth day, when the whole ear is red, hot, œdematous, and drooping, and which terminates about the twelfth day in death of the animal or recovery after more or less severe symptoms, including gangrene of the ear. Inoculation of an ear that has recently recovered from such an attack, on the other hand, leads to a transient hyperæmia, which begins a few hours after inoculation, which is never severe, and which has usually disappeared by the following day. The authors associate this milder course of the disease in the second case with the presence in the ear of inflammatory products—cells and exudation—left on the retrogression of the first attack. Alongside of these experiments may be placed those of Metchnikoff and of Issaeff, who found that if cholera vibrios or pneumonococci be inoculated into the peritoneal cavity of guinea-pigs which the day previous have been subjected to an injection of sterile bouillon, the animals recover, whereas if no preparation of the peritoneum have been made the animals succumb. It is not known if local immunity is specific, and there are many reasons for believing that this is not the case. If so, there is a marked difference between local acquired immunity and general acquired immunity.

IV. **Bacterial Factors influencing the Occurrence or Non-Occurrence of Infection.**—Besides personal factors of immunity and susceptibility the question whether inoculation of a given micro-organism shall or shall not lead to disease depends upon factors that may be grouped together as "bacterial." These are as follows:—

(i.) **The Dose used for Inoculation.**—That the dose of the causal agent of a disease which gains entrance to the tissues of an animal must have an effect in determining whether infection shall occur or no is obvious, and we have experimental evidence that such is the case. This evidence is clearest in diseases such as diphtheria and tetanus, in which graduation in severity of the symptoms can be induced in different animals by injecting graduated doses of toxin apart from micro-organisms. The same probably also holds good with injections of living bacilli, at least within limits. Upon this point Watson Cheyne has made special experiments, and he finds that in the case of each micro-organism and each species of animal there is a certain (rough) minimal number of bacteria which it is necessary to inject, otherwise infection will fail. This number is greater or smaller according to the immunity or susceptibility of the animal, to the virulence of the micro-organism used for inoculation, etc. There can be no doubt that in health, pathogenetic micro-organisms are constantly gaining access to our tissues through abrasions of the cuticular and mucous surfaces; that we do not become a prey to an infinity of diseases must largely depend upon the fact that the doses of micro-organisms that we receive in this way are subminimal.

(ii.) **The Seat of Inoculation.**—Though it is highly probable that micro-organisms cannot gain entrance to the tissues through an absolutely uninjured surface, there is reason to believe that their effects upon the body as a whole, when once they have gained entrance, depend in large degree upon the seat at which they become inoculated. Not only does this affect the general course of the disease, but it also aids in determining whether infection shall occur or no. An example of these points is yielded by diphtheria. If the micro-organism (apart from toxin) be inoculated into the peritoneal cavity of a normal guinea-pig, the animal will in a large number of cases suffer no harm, and in any case it will probably not die, but if an exactly similar inoculation be made into the subcutaneous tissue of the abdomen of another guinea-pig, it will probably die in a couple of days. The exact converse is true for *V. choleræ asiaticæ*, since a dose which, inoculated into the peritoneal cavity of a normal guinea-pig, will kill with certainty, inoculated into the subcutaneous tissues of another guinea-pig, will lead perhaps to no more than a slight local inflammation. When discussing local immunity, also, reference was made to the fact that a pathogenetic micro-organism which will lead to disease when injected into a normal part, may fail to do so if injected into a part that has a short time previously been the seat of inflammation. A satisfactory explanation of these facts is at present impossible, but they must certainly depend upon tissue conditions of some kind.

(iii.) **The Virulence of the Micro-Organism.**—Here we have another important factor in determining whether infection shall occur or no. Infection may fail because, as the result of attenuation, the microbe has become converted into a comparatively harmless parasite, or even has become unable to carry on a parasitic existence at all except under extraordinary circumstances. This is probably the case with some of the pathogenetic micro-organisms inhabiting the mouth. Attenuation of the micro-organism is probably also one of the causes for the dying-out of epidemics and for the milder course run by cases occurring towards the end of epidemics. On the other hand, the virulence of a microbe may be increased and then the liability of infection following inoculation is proportionately increased.

The virulence of a pathogenetic micro-organism may be raised or lowered by artificial means within wide limits; so that, for example, starting with a given variety of *B. anthracis*, it may, on the one hand, be attenuated to such an extent that it no longer infects the highly susceptible white mouse, and on the other hand, its virulence may be increased to such an extent that it readily kills the much less susceptible sheep. When a micro-organism has been artificially attenuated, it apparently never loses all its distinguishing properties; morphologically and culturally, its characters are practically unchanged. Probably also its original virulence may always again be established by appropriate means; as a rule, passage through one or two animals is sufficient for the purpose.

We have no evidence that a pathogenetic micro-organism ever becomes permanently saprophytic. Nor have we evidence that a normally saprophytic micro-organism ever becomes parasitic. Nevertheless, according to Klein, "*B. coli*," a saprophyte found normally in the intestine and non-pathogenetic for the guinea-pig, may, under certain circumstances, gain access to the peritoneal cavity—passing either through the injured or the uninjured intestinal wall—and may there become so virulent, that a minute dose injected intra-peritoneally into guinea-pigs produces a fatal disease which is truly infective in that it can be communicated from animal to animal. Buchner's assertion that by cultivation he succeeded in converting the common hay bacillus (*B. subtilis*) into the bacillus of anthrax has long been held as dependent upon imperfection in his methods, and in the case of Klein's experiments the great dissimilarities between the numerous varieties of micro-organism included under the name "*B. coli*" raises the suspicion that the highly virulent micro-organism may not have been derived from the harmless saprophyte at all.

(iv.) The Presence or Absence of Toxin along with

**the Micro-organisms used for Inoculation.**—Vaillard and Rouget showed that if the spores of *B. tetani*, completely freed from adhering toxin, are inoculated even in very large quantities into the highly susceptible mouse or guinea-pig, infection fails. Besson obtained similar results in the case of inoculation with toxin-free spores of malignant œdema. There is no doubt also that the effects of an injection of *B. diphtheriæ* into the peritoneal cavity of a normal guinea-pig depend very largely upon the presence or absence of toxin along with the injected bacilli. If the bacilli have been grown on gelatine, the length of time necessary for cultivation ensures that the surface of the gelatine is dry; hence the bacilli are obtained with but a small amount of adhering toxin, and in the large majority of cases injection of such bacilli is followed by no ill effects. But if the bacilli have been grown on recently prepared and moist agar-agar, or still better, if they have been grown in bouillon, a greater or less amount of toxin is injected along with the bacilli, and the effects of an intra-peritoneal injection are very different; in not a few cases death occurs in 24–48 hours.

(v.) **Symbiosis.**—Reference has already been made to the importance of symbiosis in bacteriological questions generally. Sufficient is known to indicate that symbiosis is probably a factor of the highest importance in determining the occurrence or non-occurrence of infection. In tetanus, as usually contracted through a wound to which earth has gained access, the presence of aërobic and symbiotic micro-organisms entering the wound at the same time as the tetanus bacilli or spores, is perhaps essential to the later development of the tetanus bacilli. On the other hand, it has been shown by various authors that symbiosis mitigates the course of certain infections. Thus if *B. anthracis* and *Strept. erysipelatis* be inoculated simultaneously into a rabbit, fatal anthrax is not produced, though, in the absence of an injection of *Strept. erysipelatis*, the animal would die from anthrax (Watson Cheyne, von Emmerich). The same result follows if, instead of *Strept. erysipelatis*, *B. pyocyaneus* or its products be injected simultaneously with or immediately after inoculation with anthrax (Bouchard, Charrin, Woodhead).

In infective diseases of the respiratory, the alimentary, and the genito-urinary tracts, in all of which symbiosis must be readily possible, the peculiar characters of individual attacks may well depend in part upon the accidental organisms present in the particular case. But in this matter we pass—as yet—into the region of pure speculation.

**V. On Certain Properties of Blood-Serum.**—It is now necessary to examine into certain relations obtaining between blood-serum on the one hand and bacteria and their products on the other, partly because of their intrinsic importance and partly because reference to them will frequently be made when discussing the theories of immunity. These properties are (i.) General, (ii.) Specific, and they will be described under these headings.

(i.) **General Properties.**—Blood-serum was early thought of as a medium in which the cultivation of micro-organisms might be undertaken, and its closer resemblance than other culture-media to the normal fluids of the living body promised interesting results so far as the properties of pathogenetic bacteria are concerned. But though these promises have not been falsified, in that blood-serum has been found to be the most favourable or even the only medium upon which artificial cultivation of certain micro-organisms can be carried out, the results obtained from investigation on this point have borne far more important fruit in quite another direction. For it was found that blood-serum when fresh, so far from being a favourable culture-medium for micro-organisms, in a large number of cases actually hinders their growth or positively destroys them. This germicidal property of fresh serum is gradually lost, and then the serum, like any other highly albuminous fluid, is a very suitable culture-medium.

It is not known with what constituent of the serum the bactericidal property is bound up, though Buchner, finding that the property is lost on dialysing the serum, imagined that it was in some way bound up with the salts. Indeed, beyond the facts that such a property exists, that it is lost if the serum be exposed to air and light (in which case we are probably justified in concluding that the bactericidal substance becomes oxidised), and that it is destroyed by heating the serum to 55° C. for half to one hour, we know very little. The property seems to be directed against all kinds of micro-organism, non-pathogenetic as well as pathogenetic. It is not present to the same degree in all specimens of serum, even when quite fresh, nor is it constantly found in the serum of particular species of animal; in one animal it may be present to a marked extent, and in another animal of the same species and apparently similar in all respects it may be quite absent. The germicidal substance itself is probably of an albuminoid nature and has many analogies with the enzymes. Albuminoid substances possessing bactericidal properties can be separated in an impure form from blood-serum, spleen, and tissues of most animals, and to these substances Buchner and Hankin have given the name "alexins"; according to Buchner and Hankin the germicidal action of serum is due to the presence in it of alexins. Hankin, finding that there is some relationship between the number of leucocytes present in a fluid and its germicidal value, suggested that the alexins are formed by leucocytes.

(ii.) **Specific Properties.** — Besides the possession of a general bactericidal action, specific properties may, by suitable means, be imprinted upon the blood-serum. These may be directed either against the bacteria themselves or against the toxins formed by those bacteria. Hence a serum may come to contain specific antibacterial or specific antitoxic properties, and though these properties are often intimately connected, they must, at least in some cases, be regarded as distinct. Thus Wassermann, working with *B. pyocyaneus*, found that there is a great difference in the properties of the serum yielded by an immunised animal according as it has been immunised with living bacilli or with toxin; though the animal immunised by means of toxin yields a serum possessing both antitoxic and antibacterial properties, the animal immunised with bacilli yields a serum which only possesses antibacterial properties. The same has been found in the case of other micro-organisms, so that, speaking generally, we may say that specific antibacterial properties are found in the serum of immunised animals whatever the method of immunisation adopted, while specific antitoxic properties are only found in the serum of animals in the immunisation of which toxins have, directly or indirectly, been used. The methods whereby these specific properties are conferred upon sera are those by which artificial immunity is conferred.

Antibacterial substances show many similarities with the ferments; in particular, they act in very small quantities, are probably not destroyed by drying, but are readily destroyed by heat, exposure to a temperature of 55° C. for half an hour being sufficient. They play an important part in the production of "Pfeiffer's phenomenon." Antitoxic substances are also ferment-like, but they are more resistant than the antibacterial substances and alexins. They can be dried without destruction, and they are not removed if the serum in which they are present undergoes putrefaction. According to Wassermann, exposure to a temperature of 100° C. only produces a moderate reduction in their efficiency. Antitoxic substances are of importance in that they are apparently the agents by which specifically curative and preventive sera produce immunity. With a therapeutic object a number of specific (antitoxic and antibacterial) sera has been prepared, amongst which the most important are those against diphtheria, tetanus, streptococcus infection, and pneumonococcus infection. Both kinds of anti-substance are to be found not only in the blood-serum, but to a greater or less degree in the organs and tissues of immunised animals.

(iii.) **Pfeiffer's Phenomenon.**—The appearance known as Pfeiffer's phenomenon consists in a peculiar alteration of the morphological and vital properties of certain bacteria when they are brought into contact with fluids containing specific antibacterial substances. Pfeiffer found if living and motile cholera vibrios are introduced into the peritoneal cavity of an artificially immunised guinea-pig, that the bacteria very rapidly lose their motility, adhere to one another, forming "clumps," become granular, and in the course of a short time disappear. He also found that similar appearances occur under corresponding conditions when typhoid bacilli and an animal immunised against typhoid are used. It was these experiments which led him to the recognition of the existence of specific antibacterial substances in the fluids of immunised animals. Bordet investigated the point further, and found that the same phenomenon can be obtained in the test-tube if specific immunising serum is added to a broth culture of the corresponding micro-organism. It may also be observed microscopically in the hanging drop. But *in vitro* the phenomenon does not go on to the formation of granules in the bacteria, nor to their disappearance. On the contrary, after a shorter or longer time (usually about twenty-four hours) the clumps break up, the bacteria resume their motility and they commence to multiply as they would have done in ordinary bouillon. Obviously, then, the typhoid or cholera serum produces some change in the micro-organisms and at the same time hinders their development, but it is important to notice that the serum of itself does not destroy the bacteria, at least *in vitro*. This property is not confined to the serum of specifically immunised animals, but may be seen when normal serum is used. Nevertheless when the specific serum is used the phenomenon is still recognisable if the serum be diluted with sterile broth to an extent in which non-specific serum is without effect. In the case of typhoid serum, a dilution of 1–2000 is still effective (Patella). The phenomenon is apparently a purely physical one, for Bordet showed that it may be seen when red blood-corpuscles of one species of animal are introduced into serum of another species. The phenomenon is not absolutely specific, though it is distinctive to so considerable an extent that Widal and Grünbaum severally have introduced it into clinical medicine as a means for the diagnosis of typhoid fever.

VI. **Theories of Acquired Immunity.**—It will be convenient to consider the principal theories of acquired immunity somewhat historically.

(i.) **The Exhaustion Theory.**—Long before the connection between bacteria and infective disease had been fully recognised, the immunity which is commonly seen after an attack of measles, scarlatina, or mumps was regarded as dependent upon the complete consumption of a "pabulum" by the "materies morbi." When it was found that artificial cultivations of micro-organisms whose growth has come to an end may again take on growth after the further addition of some one constituent (*e.g.*, peptone), which had lessened during the previous growth, the exhaustion theory of acquired immunity was held as strengthened. But not only was there the objection that, on this view, a separate "pabulum" would be necessary for the occurrence of each infective disease, there was the further objection that, though second attacks of infective diseases such as measles or scarlatina are rare, they are by no means unknown. In these exceptional cases an additional hypothesis was necessary to explain the re-formation of "pabulum." The theory was finally discarded when the possibility of artificial immunisation by gradual injection of toxic products—apart from micro-organisms—was demonstrated by Salmon and Smith, for consumption of pabulum by dead chemical substances was inconceivable.

(ii.) **The Retention Theory.**—Pasteur had found that the cessation of growth in a cultivation of *Saccharomyces cerevisiæ* is to be correlated with accumulation in the culture of the alcohol formed by the micro-organisms as the result of their life history. Guided by this fact Chauveau and others suggested that acquired immunity is due to storage in the body of bacterial products which prevent further growth of that variety of bacterium which produced them, though they may not prevent the growth of other bacteria. An important objection to this theory lies in the fact that acquired immunity is often of long duration, whereas the bacterial toxins, upon the accumulation of which in the system the acquired immunity is supposed to depend, are not retained for an indefinite length of time in the body but are gradually excreted, and in many instances can readily be detected in the urine. Though the retention theory of immunity is no longer held—at all events in this crude form—it is certainly nearer the truth than the exhaustion theory.

(iii.) **The Phagocytic Theory.**—This theory is bound up with the name of Metchnikoff and was gradually evolved by him from his researches upon inflammation. Metchnikoff's special training as a zoologist has influenced his whole conception of the processes of inflammation and immunity. Finding the phenomenon of phagocytosis in the highest as in the lowest members of the animal kingdom, and finding that the means whereby a lowly organism defends itself against an irritant—physical or bacterial—consists essentially in phagocytosis, he has argued that the phagocytosis seen in higher animals when subjected to the action of an irritant is equally a means of defence. So that, according to Metchnikoff, immunity to a disease implies that the phagocytes of the infected animal are able to conquer the invading bacteria, susceptibility to a disease implies that the invading bacteria are able to conquer the phagocytes.

But the phagocytic theory now held by Metchnikoff differs considerably from the phagocytic theory which he first propounded, and according to which there was a veritable combat between leucocytes and bacteria. For attack directed from the German schools and advancing knowledge have obliged Metchnikoff to assume that under certain circumstances the phagocytes become dissolved (phagolysis) in the body fluids, and lend to them chemical properties previously residing in the phagocytes alone. Nevertheless, he still maintains that the phagocytes, chiefly by phagocytosis, but partly by phagolysis, are responsible for immunity, natural and acquired.

Some of the chief objections that have been brought forward against the phagocytic theory are as follows.

(*a*) When a micro-organism is found within a cell, it is not proof that phagocytosis has occurred, for the appearances are equally explicable upon the assumption that the micro-organism has invaded the cell. In particular, in leprosy the bacilli are always found within cells, and the same is true of the gonococcus.

(*b*) Phagocytosis bears no necessary relation to the course taken by an infection or to the immunity. It is often very evident when the immunity is so slight that infection leads to death of the animal; this may readily be seen in the case of subcutaneous inoculation of the guinea-pig with diphtheria, and clinically in pyæmia.

(*c*) Phagocytosis is least evident when the micro-organism is most virulent, and when, therefore, the need of defence is greatest, and on the other hand phagocytic cells are usually most numerous and englobation of micro-organisms most common when the micro-organisms are of low virulence, and especially when large numbers of the bacteria are dead. The opponents of Metchnikoff, therefore, maintain that phagocytosis only occurs when the bacteria are dead or dying; the phagocytes are "scavengers," not "defenders."

To this criticism Metchnikoff replied that phagocytes can englobe living and fully virulent anthrax bacilli. He isolated in a hanging drop a single phagocyte containing within it a filament from a culture of anthrax, the virulence of which had been determined. This hanging drop he watched microscopically on the warm stage, and observed the filament of anthrax grow within the phagocyte, pass beyond its confines, and multiply within the hanging drop. Tested on an animal, this drop cultivation of anthrax was equal in virulence to the original culture. Though this experiment proves that a micro-organism may still be living when within a phagocyte, it proves nothing with regard to virulence. For it is known that unless a micro-organism (and especially *B. anthracis*) has been artificially attenuated throughout many generations, it readily regains its former virulence. Hence the phagocyte may have englobed a feeble bacillus, but yet that bacillus may have produced fully virulent descendants. The absence of phagocytosis when the invading micro-organism is highly virulent, Metchnikoff explained by the occurrence of negative chemiotaxis, and correlated the absence of phagocytosis with the absence of resistance to the infection.

(*d*) Destruction of bacteria occurs in fluids (such as blood-serum) from which phagocytes are completely absent. Around this question of extra-cellular destruction of bacteria controversy has been very keen, for it is obvious that with it the phagocytic theory—in its original form, at least—either stands or falls. Liakhovetsky showed that, when the corneæ of dogs are inoculated with anthrax bacilli, the microbes are invariably destroyed without any share being taken in the process by the leucocytes as phagocytes. In rabbits, also, this is true in a large number of cases, and especially in rabbits that have previously been treated with increasing doses of bacilli, with the object of obtaining a high degree of immunity. Liakhovetsky's results agree closely with those of Leber on infection of the eye with streptococci, and those of Pfeiffer on intra-peritoneal inoculation of typhoid and cholera micro-organisms in guinea-pigs artificially immunised against these diseases.

Metchnikoff was bound to acknowledge the existence of this extra-cellular destruction of bacteria, nevertheless he still sought to associate the fact with the presence of leucocytes. He assumed that the activity of the cell-free fluids depends upon "phagolysis" or solution of phagocytes in the fluid. He argued that, since intra-cellular destruction or digestion of bacteria by phagocytes must depend upon the presence within the cell of chemical digestive substances, it is readily intelligible that when the phagocytes are dissolved, the chemical digestive substances are set free, and can induce extra-cellular destruction of bacteria present in the fluid. He adverts to Bordet's work, which shows that the fluid of passive œdema (from which leucocytes have practically always been absent) and aqueous humour (which is entirely cell-free), obtained from a guinea-pig artificially immunised to cholera, are markedly less bactericidal than the blood-serum of the same animal. So also Bordet showed that if hypo-leucocytosis be induced by intra-vascular injection of finely divided carmine, the blood-serum of an immunised animal is markedly less bactericidal than it was before hypo-leucocytosis was induced. These observations, Metchnikoff believes, justify him in maintaining that immunity ultimately depends upon the leucocytes, whether those leucocytes act by way of intra-cellular destruction (phagocytosis) or extra-cellular destruction (phagolysis).

(*e*) Even if it be granted that phagocytosis is the means of defence for lowly organisms, it does not follow that this is true for higher animals. This criticism has gained in weight since the wandering cells in different animals have been more carefully studied. For a greater variety of wandering cell is found in higher members of the animal kingdom, and though in lower animals several different functions may be carried out by one kind of cell, it is possible that in higher animals there is subdivision of labour. If that be so, phagocytosis would not necessarily have the same significance in both classes, and in particular defence and phagocytosis might have nothing to do with one another. Certain authors have considered that in those animals which possess wandering cells with oxyphil granules, these cells are especially concerned with defence, the granules being secreted by the wandering cells, and consisting of a substance injurious to bacteria. This view derives some support from the fact that in such animals either finely or coarsely granular oxyphil cells are almost invariably the first to arrive at the seat of invasion by a micro-organism.

(*f*) Since the symptoms of an infective disease are essentially due to the effects produced by the action of a toxin, it follows that no theory which does not explain the neutralisation of toxin produced by a pathogenetic micro-organism, as well as the actual destruction of the bacteria themselves, can be satisfactory. Especially is this the case now that it is known that an acquired immunity can be produced by injection of increasing doses of toxins alone.[1] Metchnikoff endeavoured to meet this objection by assuming that the gradually increasing doses of toxin used in such a method of immunisation gradually "educate" the leucocytes. Hence in time, and by a survival of the fittest, a race of leucocytes is produced which is capable of withstanding the toxin produced even by virulent and living bacilli,—leucocytes, therefore, in which the strong toxin does not lead to negative chemiotaxis as it would have done had they been untrained. Since, however, this explanation only amounts to asserting that the leucocytes have acquired immunity, it cannot be regarded as an answer to the objection.

(iv.) **The Humoral Theory**.—When it was found by Fodor, and had been confirmed by Nuttall, Buchner, and other observers, that bactericidal properties reside in many fresh specimens of blood-serum, and when Buchner and Hankin isolated their so-called "alexins," it was thought that immunity, natural and acquired, might depend upon the presence of these substances in the blood. But this was soon found not to be the case:

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[1] Metchnikoff formulated the phagocytic theory before this discovery was made by Salmon and Smith.

1. Because in a large majority of cases the serum of an animal naturally immune to a particular infection does not possess any special bactericidal value against the micro-organism causing that disease. Thus the frog is naturally immune to anthrax and the hen to tetanus, but the normal blood-sera of these animals show only feeble bactericidal power against the corresponding micro-organism.

2. Because a powerfully immunising serum may, outside the body, be a highly favourable culture-medium for the same micro-organism which, by its aid, is readily destroyed in the body. Thus diphtheria bacilli grow readily on serum obtained from an animal artificially immunised against diphtheria by injection of increasing doses of diphtheria toxin.

3. Because the serum of an animal naturally immune to a particular disease does not confer passive immunity when injected into a susceptible animal.

4. Because without any alteration (or with but slight alteration) of bactericidal properties, as evidenced *in vitro*, the serum of an animal naturally immune to a particular infection may be caused to acquire properties which enable it to confer passive immunity when injected into a susceptible animal.

The last two statements are supported by the following experimental data. F. Klemperer found that the serum of rabbits which are naturally immune to *B. murisepticus* and *B. pneumoniæ* (Friedländer) does not protect susceptible animals, but that it may be rendered protective against the corresponding disease if the rabbit be subjected to increasing doses of either of these bacilli previous to the removal of its blood. Vaillard showed that though the serum of the hen, which is naturally immune to tetanus, cannot confer passive immunity to tetanus when injected into animals susceptible to that disease, it becomes capable of doing so if the hen has been previously injected with increasing (and enormous) doses of tetano-toxin.

It was obvious, therefore, that a purely humoral theory of this description is insufficient, that natural immunity cannot be explained by the presence of "alexins" in the blood nor acquired immunity by an increase in the amount of those "alexins."

(v.) **The Cellulo-Humoral Theory.**—In one or other form this theory of acquired immunity has the greatest number of adherents at the present day. According to it, the immunity is indeed due to substances which are present in the blood of the immunised animal and are recognisable in the blood-serum, but they are not present there alone, since they exist in all the tissues and juices. These substances are considered as being formed by the cells of the body during exposure, and for a longer or shorter period after cessation of exposure, of those cells to the stimulus of the specific micro-organism or its toxin; they are not formed by one specific variety of cell, whether phagocyte (Metchnikoff) or oxyphil cell (Buchner, Hankin), but in greater or less degree all varieties of cells combine to produce them. The protective substances being present in the fluids of the body, they act upon the bacteria and their toxins in the fluids of the body, *i.e.*, the processes of acquired (and passive) immunity are essentially extra-cellular. Hence on this theory, though acquired immunity ultimately depends upon the functional activity of cells, these cells do not act as phagocytes (this being quite an unimportant phenomenon so far as immunity is concerned) but rather as secreting organs, which, according as they have been stimulated by bacteria, produce specific antibacterial substances, or as they have been stimulated by toxins, produce specific antitoxic (and antibacterial) substances.

The cellulo-humoral theory accords well with certain observed facts. It explains acquired immunity both to toxins and to bacteria, however that immunity is produced; to toxins, because it has been found that the amount of antitoxic substance produced (the antitoxic value of the serum) varies within rough limits directly as the amount of toxin used for the production of the immunity (Roux); to bacteria, partly because it has been found that in the animal body antitoxic substances are associated with destruction of the bacteria for which they are specific, partly because, if the acquired immunity be produced by the aid of bacteria, it has been found that specific antibacterial substances are present in the serum of the immunised animal. It explains in the simplest way those cases in which destruction of bacteria takes place in the animal body without the obvious intervention of leucocytes, and those cases in which immunity is absent or relatively slight in spite of the fact that leucocytes are present in great numbers at the seat of infection. It explains the possibility of passive immunity; for since the "anti-substances" to a given infection are present in the blood-serum of an animal, actively immunised by whatever means to that infection, transference of the blood-serum to a susceptible animal implies transference of the anti-substances and transference with them of the protective and curative properties which are bound up with those anti-substances. It explains in the same way the transmission of immunity from mother to child, whether through the placental circulation or through the milk. It explains the rapid loss of passive and of transmitted immunity; for since the cells of the body only form specific anti-substances when they have been stimulated thereto by specific toxin or bacteria, and this condition is absent in passive and in transmitted immunity, the amount of anti-substance in the recipient of the serum is not undergoing constant renewal, but on the other hand is undergoing constant loss owing to its removal in the excretions.

But even if we accept the cellulo-humoral theory there are difficulties with regard to acquired immunity which are still unexplained. Why do toxins and bacteria, which are present in an animal for a limited time only, cause the cells of that animal to produce specific anti-substances for, it may be, scores of years? why are the sera specific? how do the anti-substances produce immunity? what is the origin of the anti-substances? is the recipient of the serum in "passive" immunity a *passive* agent, or do his cells play a part in determining the occurrence of immunisation in him? if phagocytosis is unimportant, so far as immunity is concerned, why is it so commonly observed in association with processes of immunisation? These are all questions of moment, and to them a few words will now be devoted; questions which are at present only of speculative interest will be neglected.

*The Specificity of Sera.*—It is generally accepted that acquired immunity is specific, that is to say, an immunity conferred by one or other method obtains only against the particular micro-organism which, or the toxin of which, has been used in conferring the immunity. So that, for example, an animal immunised against diphtheria is not at the same time immunised against tetanus or *vice versa.*

Conversely, a given bacterium or its toxin can only confer immunity against itself. For a short time there was doubt on this point raised by experiments made by Klein and supported by others made by Sobernheim and by Hueppe. Klein believed that he had obtained an immunity against cholera by injections of *B. pyocyaneus*, *B. prodigiosus*, and a variety of other micro-organisms, an immunity against *B. prodigiosus* by injection of *B. pyocyaneus*, an immunity against *B. pyocyancus* by injection of *B. prodigiosus*, and so on. But since the peritoneal cavity was the seat of inoculation throughout Klein's experiments, there is no doubt that Pfeiffer's observation that the preceding inoculation leads to a leucocytosis is the real explanation of the apparent immunity. We have here, indeed, a special example of local immunity or increased non-specific resistance. Kanthack and Wesbrook also repeated Klein's experiments and showed that, though a certain amount of immunity is conferred by injection of *B. prodigiosus* against *B. pyocyaneus*, and *vice versa*, the immunity is neither so pronounced nor so lasting as when the same micro-organism is used for immunisation and for testing immunity.

But though immunity is specific and in many cases specific to a remarkable extent, it is not quite exclusive. For instance, many varieties of vibrio are associated with Asiatic cholera, and though in many cases immunity conferred on animals by one variety is only shown to inoculations with that variety, this is not always the case; for often a certain amount of interchangeability exists, though the highest degree of immunity conferred by any particular variety of vibrio is shown against inoculation with that particular variety. This specificity of sera and its limitations are well seen when cultivations of the vibriones are mixed with immunising sera from different sources in testing the presence or absence of Pfeiffer's phenomenon.

It is quite unknown how this reciprocity between specific bacteria or toxins and their corresponding antibacterial or antitoxic substances is brought about, though the specificity of the sera must in some way depend upon changes induced or undergone by the bacteria and their toxins. Some authors (Marmier, Smirnow, Kruger, and others) have asserted that antitoxin can be directly formed from toxin by the action of electricity; Roux pointed out that the amount of antitoxin formed is roughly proportionate to the amount of toxin used for producing immunity; Klein, that intra-peritoneal injection of diphtheria bacilli free from toxin is followed by the formation of antitoxin in the animal; Dzierzgowski, that if toxin be injected into a certain part, and the amount of antitoxin in that part be estimated a little later, there is a local accumulation of antitoxin. All these experiments seem to indicate that the anti-substances are formed by conversion of the bacteria or their toxins, and no doubt if this be the case it is easier to comprehend the specificity of immunity. But Roux showed that if, during active immunisation of an animal against diphtheria, the animal be bled and the antitoxic value of its serum be estimated, and if, *without any intermediate injection of toxin*, the animal be again bled a little time later, the antitoxic value of its serum may be found to have increased in the interval between the two venesections. This fact and the fact that acquired immunity persists long after the specific bacteria and their toxins have completely left the body, raise doubt whether so simple an explanation of the specificity of immunity as that which regards it as being due to the conversion of bacteria and bacterial toxins into antibacterial and antitoxic substances is justifiable. It seems far more probable that we may have here an example of the much debated "inheritance of acquired characteristics."

*Mode of Action of Anti-substances.*—There can be no doubt, though the anti-substances are formed through the agency of cells that the substances themselves are purely chemical; hence the immediate mechanism of immunity must be chemical also, though possibly of a very complicated nature. Behring regarded toxin and antitoxin as neutralising one another somewhat after the fashion of an acid and an alkali, and Ehrlich has recently brought forward evidence in favour of this view. He finds, for example, that exact neutralisation of ten times the minimal fatal dose of diphtheria toxin can be obtained so long as the dose of anti-diphtheritic serum which is necessary to neutralise a single minimal fatal dose of toxin is also multiplied by ten. The same is also true if the multiplier in each case be one hundred instead of ten. If these corresponding quantities of serum and of toxin be mixed in a test-tube, and the mixture injected into a normal guinea-pig, the animal does not suffer from diphtheria. He found that the same law of multiples obtains in the cases of abrin, ricin, tetano-toxin, and their corresponding sera. It would seem from these experiments that the toxin and the antitoxin neutralise one another, with the formation of a harmless substance.

But there is much experimental evidence against such a view. Buchner found that a mixture of tetano-toxin and anti-tetanic serum which is harmless for the white mouse is not harmless for the guinea-pig, which, on the contrary, dies from tetanus. Roux and Calmette showed that snake poison is not directly destroyed by the serum of immunised animals. If they heated a mixture of poison and serum which was without action in the animal body, for a long time at 68° C., the protective power of the serum was neutralised, but the poison acted as vigorously as if it had never been in contact with the serum. Perfectly similar results were obtained by Wassermann with the toxin of *B. pyocyaneus* and its corresponding serum. After boiling a mixture of the two substances which was harmless to animals, the protective power of the serum was annihilated, but the toxic action remained. Fresh addition of serum after the boiling caused the toxic action to again disappear, which shows that the true poison of pyocyaneus was present, and not some secondary toxic substance formed by boiling the poison and the serum together. In the case of *B. pyocyaneus*, Wassermann distinctly found that the doses of toxin and of serum injected into an animal cannot be increased *ad libitum* without harm to the animal, as should be the case if the poison and serum produced a harmless mixture, and as Ehrlich asserts is the case with diphtheria toxin and anti-diphtheritic serum. Actually Wassermann never succeeded in rendering more than six times the minimal fatal dose of pyocyaneus poison harmless in the body, however great the amount of immunising serum he injected at the same time.

Wassermann believes that the case is even more strong against the conception of a neutralising action on the part of the antibacterial substances. Even when the dose of pyocyaneus serum (which contains antibacterial substances) is increased out of all proportion to the increase in number of bacilli used for inoculation one cannot go beyond a certain point. Thus, though ·01 c.c. of a certain immunising serum completely destroyed one platinum loopful of a living culture of *B. pyocyaneus* in the animal body, 1 c.c., or a hundred times the amount of serum, could not produce the same result when three loopfuls of a living culture were introduced into the animal. The animal succumbed in spite of the fact that it still contained so much immunising serum that ·2 c.c. of the peritoneal exudate of the dead animal, together with the bacilli which that exudation contained, if injected into a fresh animal, not only killed the bacilli already present in the exudation, but also a further half-loopful of a fresh living culture in addition. Wassermann explains his results by assuming that the antibacterial and the antitoxic substances act by inducing a reaction on the part of the cells of the animal into which they are injected, and that it takes a certain length of time for the reaction to be brought about. There is no doubt that if his experiments are correct (and they are so important as to need repeated corroboration by other observers) they constitute a formidable obstacle to acceptance of the neutralisation view.

At the present time, therefore, we must confess to complete ignorance as to the mode in which the antibacterial and antitoxic substances produce immunity, whether the immunity be active or passive. Concerning natural immunity we are if possible more in the dark. Less work has been done on the subject, and it can only be said that the alexin theory of Buchner and Hankin and the phagocytic theory of Metchnikoff, both of which have been put forward as explanations, are unsatisfactory.

With regard to the part played by phagocytosis in questions of immunity, it is possible that supporters of the cellulo-humoral theory have been too exclusive. It is certain that phagocytosis is one of the most prominent phenomena accompanying immunisation processes, and though we undoubtedly meet with cases in which phagocytosis is absent when we might expect it present and *vice versa*, we are far from understanding the underlying conditions of phagocytosis. There is certainly no reason to hinder our believing that phagocytosis gives the *coup de grâce* when the antibacterial and antitoxic substances have weakened invading bacteria by altering their bodies and by depriving them of their great weapon, the toxin. It is not unlikely that in the near future the theory of immunity gaining most acceptance will be a compromise between the phagocytic and the cellulo-humoral theories. Already Metchnikoff has taken the first step towards reconciliation.

VII. **Latency in Infective Disease.**—It has long been held that disease may sometimes be latent. That is to say, though infection has been received at a certain time, the manifestation of symptoms of the disease is postponed for a longer or shorter period. Latency of disease was made the subject of discussion at the Royal Medical and Chirurgical Society in 1896, and clinical instances of latency in tuberculosis, in syphilis, in leprosy were brought forward by different speakers. But the difficulty in all cases of latency is to ensure the absence of any intermediate but unrecognised infection, so that the best examples of latency for our purpose were those brought forward by Dr Phineas Abraham and occurring in leprosy. Abraham mentioned the case of a man who became leprous forty years after his last exposure to the disease. During this period of forty years the man had resided in England continuously and had held no communication, even by letter, with lepers or regions in which leprosy is endemic. So far as it is possible to ensure absence of intermediate infection, it is excluded in this case, and we must therefore allow that leprosy bacilli were introduced into the body of the man at least forty years before he manifested the disease, and that during that period or the greater part of it they were latent.

Now we may have in latency a special form of incubation, and though an incubation period of forty years is excessive there is no theoretical objection to its possibility. Upon that view the infective agent must have been multiplying and forming toxin, though the amount of toxin formed was insufficient to lead to symptoms over all that period. But on the other hand it is possible that though the micro-organisms were present in the body of the man they were in an inert condition: their development was arrested, but they remained capable of growth. We cannot decide between these two possible explanations, but it is certain that the latter condition can be observed in nature.

In the disease of silkworms known as "pébrine," the micro-organisms which cause the disease can actually be seen in the eggs laid by an infected moth. In spite of the fact that the eggs are kept under conditions by no means unfavourable to the growth of the micro-organism, the micro-organisms in the eggs do not commence to develop until the changes occur which lead to the formation of a caterpillar. So long as the germ of the caterpillar is quiescent the micro-organisms are latent, capable of development but not developing, but so soon as that especial change in their environment which is caused by the formation of the caterpillar takes place, their development proceeds apace. Hence the possibility of a strict latency (as distinguished from an undue prolongation of incubation period) in infective disease must be allowed. It is well known how the development of a micro-organism even upon artificial media is influenced by minute changes in the constitution of the nutrient medium, and it is quite conceivable that the balance between the micro-organism on the one hand, and the tissues into which it gains entrance on the other, may at times be such that the micro-organism neither dies nor exercises its vital functions, but remains, so to speak, in a state of suspended animation and capable of development if, at any time, the opposing force exercised by the tissues becomes lessened. In this connection it is a remarkable fact that clinically "latent" disease almost always becomes manifest at a time when the patient has been subjected to depressing conditions of some kind.

VIII. **The Pathology of Relapses.**—A relapse is said to occur when a patient, during convalescence from an attack of an infective disease, again suffers from a fresh attack of the same disease; frequently, however, a sudden aggravation of receding symptoms or the supervention of complications is designated by the same term. The best examples of relapses are seen in relapsing fever, in typhoid fever, and, it might almost be said, in the successive attacks that occur in malaria.

The explanation of relapses is by no means easy. That the relapse is really a fresh attack of the disease is shown by the facts that in each relapse of relapsing fever the micro-organism is recognisable in the blood, though in the intervals it cannot be found, while the symptoms of the first attack are repeated in subsequent attacks; that what has just been said for relapsing fever is true also for successive ague-fits in malaria (if we include successive ague-fits under the heading of relapses); and that in typhoid fever a relapse is ushered in by the same characters of the patient's temperature as are found in the initial attack, while all the phenomena of a primary attack, including the cutaneous eruption, may be observed.

It is therefore necessary to explain not only re-infection but also re-infection at a time when, by our conceptions of the reasons which lead to convalescence, the patient has acquired a certain degree of immunity. The re-appearance of symptoms obviously depends upon the fact that fresh toxic substances are enabled to manifest their effects, though perhaps the cases of relapsing fever and malaria—in which it is not known that toxic substances are formed—forces us to add to the words "fresh toxic substances" the words "fresh micro-organisms." The differences that, there is reason to believe, obtain between the modes in which the micro-organism of typhoid fever on the one hand, and those of relapsing fever and malaria on the other, produce symptoms, must also play their part.

Now in typhoid fever Chiari has shown conclusively that the typhoid bacilli gain access to the gall-bladder. Out of 22 consecutive cases of this disease he found typhoid bacilli in the gall-bladder in 19, and in 15 of these, in pure culture. In 13 of the 19 cases in which there was a positive result, the gall-bladder was inflamed, showing hyperæmia, œdema, and infiltration of its walls with small cells. These conditions are such that we can easily conceive the bacilli as being at times locked up in the gall-bladder, multiplying there and forming their toxic products, but unable to find an exit for themselves or their products owing to congestive and inflammatory obstruction of the cystic duct. If, then, for some reason the duct becomes patent, micro-organisms and products can be discharged into the intestine. But under these circumstances the dose that would be discharged into the intestine would be relatively very large, and though a certain degree of immunity to typhoid might be present owing to the previous attack, it might not be sufficient to prevent the manifestation of symptoms when the dose injected is thus large. We have an exact parallel to this in immunisation experiments. It is a matter of common experience that during the immunisation of an animal, *e.g.*, the horse against diphtheria, injection of an excessive dose of toxin or of living bacilli can lead to symptoms of the disease against which we are increasing resistance, even though before injection of the excessive dose, the serum of the animal had by previous treatment attained to a certain and perhaps a high immunising value. Nevertheless such an explanation must only be regarded as possible. Many of the conditions associated with relapses are unknown and others are so obscure that nothing more than suggestions can at present be offered.

*Note.*—In reference to the dilution of "typhoid" serum and the occurrence of agglutination (p. 401), Durham announced at the Royal Medical and Chirurgical Society (Jan. 11, 1898) that he had found a highly potent serum still efficacious in a dilution of one in two millions.

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For fuller references on the subjects contained in this chapter see KANTHACK, Allbutt's System of Med., vol. i., Art. "The General Pathology of Infection."

# CHAPTER X.

## THE PATHOLOGY OF HEAT REGULATION.

*Synopsis.*

I. General Considerations.
    (i) Heat Production.
    (ii) Heat Loss.

II. Normothermia.
    (i) Variations in Temperature Compatible with Normality.
    (ii) The Means whereby Heat Regulation is carried out.
    (iii) Metabolic Changes associated with Normal Heat Production: the Respiratory Quotient.

III. Hyperthermia.
    (i) From continued Exposure to High External Temperature.
    (ii) From Cerebral Lesions.
    (iii) Following Administration of certain Drugs.

IV. Hypothermia.
    (i) From continued Exposure to Low External Temperature.
    (ii) In the Course of Disease.
    (iii) Following Administration of Drugs.

V. Fever or Pyrexia.
    (i) Characters of the Temperature.
    (ii) Anatomical Changes in Fever.
    (iii) Functional Changes in Fever.
    (iv) Metabolism in Fever.
    (v) Ætiology of Fever.
    (vi) Antipyretics.
    (vii) The Theory of Fever.
    (viii) The Meaning of Fever for the Economy.

**I. General Considerations.**—It is only by comparison of the abnormal with the normal that a proper conception of any morbid process can be obtained, and in the case of heat regulation this course is especially necessary. For in the first place, though abnormal temperatures are often associated with well-marked anatomical, metabolic, and functional changes on the part of the patient, yet the processes of pathological heat regulation (considered apart from such changes in the patient) often differ from the processes of physiological heat regulation more in degree than in kind; and in the second place, certain of the variations in heat production, heat loss, etc., consistent with health, are themselves so wide that consideration of one factor alone, even though it occurs along with disease, may be quite insufficient to determine whether that factor is physiological or pathological.

The great difference between cold-blooded and warm-blooded animals consists in the fact that whereas the internal temperature of the former varies with the temperature of the medium in which they are placed, the temperature of the latter practically remains constant, in spite of wide variations of the external temperature. Hence *regulation* of internal temperature—as we understand the term—only obtains in warm-blooded animals: and with these alone, unless definite statement to the contrary is made, we shall be concerned in the following pages.

The fact that in cold-blooded animals the nervous system is of a lower order than it is in warm-blooded animals, of itself suggests that the nervous system plays a part in determining the difference between their methods of reaction to variations in external temperature, and this suggestion is supported by experimental and clinical evidence; for lesions of the brain and spinal cord in warm-blooded animals can be followed by alterations of temperature, and in particular by an approximation of the warm-blooded animal, so far as reaction to changes in external temperature is concerned, to the cold-blooded type. The nervous system may be concerned with heat regulation in several ways, direct and indirect, and to these reference will be made later.

(i.) **Heat Production or Thermogenesis.**—Since the chemistry of life so largely consists in the breaking down of complex into simpler molecules and in the oxidation of these, during both of which processes heat is set free, it is clear that we must look for the seats of heat production in those regions where chemical changes of these natures are most evident. Of these regions the muscles, the alimentary canal, and the glands are of most importance.

In normal life and upon a normal diet the heat produced ultimately comes almost entirely from combustion of the food consumed. Not indeed that the amount of heat produced can be increased indefinitely by augmenting the food consumption, for when the quantity of food ingested exceeds a certain amount it is not directly broken up, but is stored up in an easily oxydisable form as fat. But it is found, when neither fat is being laid on nor the body is wasting, that the total heat production of the body in a given time as measured directly, equals the sum of the heat values of the various substances consumed during the same period *less* the sum of the heat values of the excreta and unabsorbed portions.

The heat values of different food-stuffs have been determined by a number of authors and recently with great precision by Rubner. According to Rubner the number of kilocalories yielded by the classes of food-stuff is as follows—

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 gram proteid yields | 4·1 | kilocal. | (gross[1]) | and | 3·2 | kilocal. | (net[1]). |
| 1 gram fat yields | 9·3 | ,, | ,, | ,, | 8·4 | ,, | ,, |
| 1 gram carbohydrate yields | 4·1 | ,, | ,, | ,, | 3·8 | ,, | ,, |

From these values the heat value of any diet may be determined. Thus an ordinary diet for an adult, consisting of 120 gm. proteid, 60 gm. fat, 500 gm. carbohydrate, yields the following amount of available heat—

| | | | |
|---|---|---|---|
| 120 grams proteid | × 4·1 = | 492·0 | kilocal. |
| 60 grams fat | × 9·3 = | 558·0 | ,, |
| 500 grams carbohydrate | × 4·1 = | 2050·0 | ,, |
| | | 3100·0 | kilocal. |

(*a*) *Heat Production in Muscle.*—We know that the contraction of a muscle is associated with the formation of $CO_2$[2] and of various nitrogenous and other substances less complex than proteid, and we might therefrom conclude, what we know on other grounds to be a fact, that the muscles are a seat of heat production. Though a muscle, considered as a machine converting potential energy into work and heat, is more economical than the best devised steam-engine, yet at a low computation four-fifths of the potential energy set free in causing a contraction is given out as heat. The large proportion of the body weight which is formed by the muscles, and the constancy with which muscular contraction is going on even during rest, indicates that the muscles must be a highly important seat of heat formation. It has been calculated by different observers that the total heat produced by the heart during the twenty-four hours may amount to 100–300 kilocalories. Since Helmholtz estimated the total heat loss from the clothed surface of an adult in twenty-four hours as about 2700 kilocalories, it is obvious that the heat produced by heart action alone can cover a not inconsiderable portion of that loss.

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[1] The gross values are those yielded by complete combustion of the given substance, but in the case of proteid the value given (4·1) is that of the heat value less the heat value of the urea, uric acid, ammonia, etc., that are formed; if these be not deducted the heat value of proteid is 5·5 kilocalories. The net values are those which are physiologically produced after all deductions for non-absorption, etc., have been made. A calorie = the amount of heat necessary to raise the temperature of 1 gram of water 1° C.; a kilocalorie is, of course, one thousand times that amount.

[2] See note, p. 125.

(*b*) *Heat Production in Glands.*—Concerning heat production in glands we are more uncertain, for though there is no doubt that in glands many complex and extensive chemical processes are going on, yet in some of these, especially those which are synthetical, heat must be absorbed. Hence it is difficult to say on which side the balance will be. Nevertheless both Ludwig and Claude Bernard asserted that the submaxillary saliva of the dog is warmer than the blood in the carotid, and Grijns found that the urine immediately on its arrival in the pelvis of the kidney is hotter than the blood in the aorta. The fact, too, that the temperature of blood in the hepatic vein of the dog (38·4°–39·7°) is higher than that of the blood in the portal vein (38°–39°) argues for the production of heat in the liver. Bayliss and Hill, however, have recently (1894) reinvestigated the subject and failed to find evidence of any formation of heat in the salivary glands by any known method of measuring variations in temperature. This result no doubt depends upon the small size of the glands and the rapidity of their circulation.

(*c*) *Heat Production in the Alimentary Canal.* — It must clearly be recognised that the heat produced in the alimentary canal is only one portion of the heat yielded by the food. For though disintegration of food occurs during the processes of digestion in the alimentary canal, the *final* disintegration takes place in the tissues of the body generally and in the muscles in particular. When, therefore, it was said above that "the heat produced comes from the food consumed" it must not be understood that changes of the food in the alimentary canal alone are meant, but rather changes which go on in various parts of the body until the complex "food" has been reduced by this tissue and that, to its lowest form. A large proportion of the heat produced in the alimentary canal is, of course, produced in the muscles which are connected with this tract. A certain amount of heat is no doubt produced by the fermentative and other changes undergone by the food in the alimentary canal as the result of bacterial action, but of this we have as yet no measure.

(ii.) **Heat Loss or Thermolysis.**—The principal seat of heat loss is the skin, which, being normally—except in the tropics—of a higher temperature than the surrounding air, constantly gives up heat by conduction and radiation. In those animals in which sweat glands are well developed, the heat lost by evaporation is of equal if not of greater importance. Heat is also lost to the body by respiration, for the air which enters the lungs is—again except in the tropics, and under extraordinary circumstances—cooler than that which leaves them, and the difference is supplied by the heat of the body. Since expired air is almost completely saturated with moisture, evaporation from the respiratory tract also plays an important part in thermolysis. The amount of heat lost by respiration, like the amount lost by radiation and conduction from the skin, no doubt varies inversely with the external temperature, so long as that temperature is lower than the temperature of the animal. Of the total heat lost by the body it has been estimated that about 80 per cent. is lost by the skin and about 20 per cent. by the lungs. Such loss as is due to warming of ingested food, to heat lost along with fæces and urine, is relatively so small that it may be entirely neglected.

II. **Normothermia.**—(i.) **Variations in Temperature Compatible with Normality.**—The heat produced in the muscles, etc., and the heat lost by the skin, etc., are so balanced that in warm-blooded animals a relatively constant temperature results. This temperature, however, is not absolute for all varieties of warm-blooded animals, nor are the limits of variation consistent with health the same in all animals. The following values are given by Richet as the mean temperatures of certain animals:—

| | | | | | |
|---|---|---|---|---|---|
| Man, | 37·0° C. | (98·6° F.) | Sheep, | 39·5° C. | (103·1° F.) |
| Ass, | 37·4° C. | (99·3° F.) | Pig, | 39·7° C. | (103·3° F.) |
| Horse, | 37·7° C. | (100·0° F.) | Wolf, | 40·5° C. | (104·9° F.) |
| Monkey, | 38·1° C. | (100·6° F.) | Falcon, | 40·5° C. | (104·9° F.) |
| Cat, | 38·8° C. | (101·8° F.) | Hen, | 42·2° C. | (108·0° F.) |
| Dog, | 39·0° C. | (102·2° F.) | Raven, | 42·8° C. | (109·0° F.) |
| Guinea-pig, | 39·1° C. | (102·4° F.) | Sparrow (Summer), | 43·7° C. | (110·7° F.) |
| Rabbit, | 39·5° C. | (103·1° F.) | | | |

The limits of variation consistent with health are not known for all these animals, but that the limits are in some cases very wide is shown by the following examples. They are taken principally from Pembrey's article on "Animal Heat" in Schäfer's *Physiology for Advanced Students.*

| | | | |
|---|---|---|---|
| Man, | 36·15°–37·8° C. | Guinea-pig, | 37·0°–39·2° C. |
| Horse, | 36·1° –38·6° C. | Rabbit, | 37·0°–40·8° C. |
| Monkey, | 36·9° –39·7° C. | Sheep, | 38·5°–41·8° C. |
| Cat, | 37·9° –39·7° C. | Pig, | 38·7°–40·8° C. |
| Dog, | 37·1° –39·9° C. | | |

Besides the limits which have been given above, the temperature of man (and probably also that of all other warm-blooded animals) undergoes diurnal variations, the highest point (about 37·5° C.) being reached between 5 p.m. and 7 p.m., the lowest (about 36·4° C.) between 4 a.m. and 7 a.m.. The normal diurnal range therefore is 1–1·5° C. Apparently this diurnal variation depends upon activity and feeding during the daytime, for Mosso and others have shown that the curve tends to become inverted if the individual works and feeds at night and sleeps during the day. Nevertheless, the careful observations of Hoover and Sollmann, made hourly upon a hypnotised fasting man for eight consecutive days, show diurnal variations of approximately the ordinary kind. Diurnal variations are therefore not dependent upon these factors alone.

Now the constancy of temperature—using that term in a broad sense—that obtains in warm-blooded animals obviously depends upon the existence of a direct ratio between heat production and heat loss. Were the heat produced even under ordinary circumstances, by the chemical processes continually going on in the body, to accumulate without heat loss, the temperature of the individual in twenty-four hours would be raised by about 48° C., an amount which would be incompatible with life, if for no other reason than because of the coagulation of the body-proteids to which it would lead. The normal loss of heat prevents this from taking place, but were a healthy individual to undergo excessive muscular exertion with its corresponding increase in heat production, while his loss of heat though "normal" remained unaltered, his temperature would infallibly rise. In the same way, if the heat loss obtaining under conditions of rest at a temperature of 15° C. were to obtain also when the individual, still kept at rest, was placed in an atmosphere at 0° C., his temperature would infallibly fall. Neither of these contingencies would actually arise; in the first case, because the individual would increase his thermolysis, and in the second case, partly because he would diminish thermolysis, partly because he would increase thermogenesis.

But though the failure of a rise of internal temperature in a case where an abnormal amount of heat is being produced must of necessity depend upon a proportionate increase in heat loss, it does not follow that the absence of a fall in temperature of an individual on exposure to a low external temperature depends alone or at all upon a diminished loss of heat. The heat loss may in this latter case remain the same, or even be increased, and yet the temperature of the individual will be maintained if he produces a proportionately greater amount of heat. Such a condition as this can be well seen in the case of athletic sports undertaken during the winter. The temperature of the air being greatly below that of the skin, and the tendency to cooling of the body being great, one might expect that such mechanisms as diminish heat loss would be called into play, but the flushed condition of the skin and the increased rapidity of respiration are evidence that if the heat loss were not increased, the increased heat production in the muscles would not only maintain the normal temperature, but cause an actual rise.

Though, theoretically, regulation of heat production in correspondence with heat loss, or regulation of heat loss in correspondence with heat production, would either of them, alone, suffice for the maintenance of an even temperature, this end is attained in warm-blooded animals not by means of either the one or the other process alone, but by the interaction of both. The advantage to the economy of such an interaction is manifest, and when it is recognised that there are limits both to thermogenesis and to thermolysis, it is clear that without such interaction the range of external conditions under which existence would be possible would be seriously contracted.

The constancy of temperature observed in a healthy individual from day to day being dependent upon an equilibrium between his heat production and his heat loss, it is necessary that the seats of these two processes should be brought into close relationship with one another. This connection is made by the blood. The heat formed in muscles and glands is conveyed away from these parts by the blood which circulates through them, and goes to heat the superficial parts; the blood from which heat has been removed during its passage through the skin and lungs goes to cool the heat producing tissues. Hence there is always a tendency for the production of one uniform temperature throughout the body. Nevertheless, perfect uniformity of temperature is never attained during life. The temperature of deeper parts is always higher than the temperature of more superficial parts; thus the temperature in the rectum is ordinarily about half a degree higher than that in the mouth or in the axilla, and a variable number of degrees higher than that of exposed superficial parts. In many cases the temperature of deeper parts is higher than that of exposed superficial parts by a very considerable number of degrees (7° F. or more). This great difference, however, does not depend so much upon a rise of internal temperature as upon a fall in superficial temperature, for the deeper parts are protected from those conditions of external temperature which are capable of inducing a marked fall in surface temperature. Nevertheless, in fever the difference between internal and superficial temperatures may be great, not only because the surface is cooler, but also because at the same time the deep parts are warmer than normal.

(ii.) **The Means whereby Heat Regulation is carried out.**—The means whereby heat regulation is carried out are many and different. It will be necessary to consider them (*a*) when heat loss is to be increased, (*b*) when heat loss is to be diminished, (*c*) when heat production is to be increased, (*d*) when heat production is to be diminished. Each of these will be briefly dealt with.

(*a*) When heat loss is to be increased the seats of heat loss become congested, and the functions connected with those parts are exercised to a greater extent. Thus the skin becomes red and hot, and the sweat glands secrete with greatly increased vigour, the rate of respiration is increased, and such natural means of warming the air before its entry into the lungs as respiration through the nose, are no longer utilised; the animal breathes rapidly with widely open mouth, and the inspirations are shallower than normal. His heart beats more rapidly and quickens the blood-stream in the dilated peripheral blood-vessels. He exposes as much of his surface to well conducting materials as possible: if human, he discards clothing, if lower animal, he stretches himself out at full length and brings as much of his body in contact with the ground as possible. At the same time, by a cessation of voluntary muscular action he reduces heat production to a minimum.

(*b*) When, on the other hand, loss has to be diminished, the blood-vessels of the skin contract, the skin becomes pale or even bluish, while the sweat glands, in those animals possessing them, cease to secrete. If human, he assumes a crouching position and, aiding nature by art, wraps himself in badly conducting material, or lights a fire to diminish the difference between his own temperature and that of the external air. If lower animal, he assumes a crouching position, while the hair, feathers, or fur "stands on end" and by the increased amount of dry air which it holds between its meshwork, surrounds the animal with a greater thickness of badly conducting material.

At the same time he increases his heat production by the various means about to be described.

(*c*) When heat production has to be increased, the animal makes use of the two sources of heat production, muscular action and food. He becomes more active in his movements, runs, leaps, and, in addition to these voluntary actions, he may shiver, shivering being probably the natural means whereby heat production is increased; he takes more food, and especially fats, for long before physiology had demonstrated that the heat value of fat is high, the dweller in northern regions, such as the Eskimo, had learnt the fact by practical experience. At the same time he diminishes heat loss as far as possible.

(*d*) When heat production has to be diminished, the animal acts in the opposite manner. He ceases to exert himself and eats little. The indolence and capricious appetite of dwellers in tropical countries have their physiological meanings in connection with heat regulation.

Of the means that have been described, the vascular, cardiac, and hidrotic obviously depend upon the nervous system. But in addition to these means, which we may call *indirect*, there is reason to believe that the nervous system exerts a direct influence upon heat production at least. For in the neighbourhood of the crucial sulcus (Wood) and of the corpus striatum (Aronsohn and Sachs) there are regions, injury of which leads to an increase of temperature (in man on the other side of the body) apart from obvious vaso-dilatation, and with the coexistence of muscular paralysis.[1] Claude Bernard, from experiments on the rabbit's ear after section of the cervical sympathetic, concluded that there are definite nerves controlling temperature (*nerfs calorifiques, nerfs frigorifiques*). But though, from the discoveries of Wood and Aronsohn and Sachs, we are perhaps led to believe in the existence of cerebral heat centres,[2] which may be independent of motor centres and vaso-motor centres, the existence of special nerves is very uncertain. Though we must probably acknowledge the existence of special impulses in connection with heat production, the paths by which those impulses travel cannot be separated, at present, from those along which motor and vaso-motor impulses travel.

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[1] Curare, given in moderate doses, has been said to lead to no fall of temperature, sometimes even to a rise, in spite of the muscular paralysis to which it gives rise (Högyes, Mosso), but this is doubtful, *cf.* p. 442.

[2] For a criticism of the current view as to the existence of definite thermogenetic centres, see Pembrey's article on "Animal Heat" in Schäfer's *Physiology*.

It is uncertain how the peripheral changes which lead to the constriction or dilatation of blood-vessels are brought about. One is naturally inclined to regard the vascular change as a reflex act, and the central and efferent portions can easily be localised in the vaso-motor centre and in the vaso-motor nerves, but with regard to the afferent nerves we are in doubt. Heidenhain found that electrical and mechanical stimulation of sensory nerves and of the cord lead to a rise of central blood-pressure and a fall of central temperature, and thence concluded that the vaso-motor and the thermo-regulatory centres are distinct, but neither his results nor his conclusions have escaped adverse criticism. The question is far from a simple one. The author has shown that in the mouth, local application of heat raises the temperature of the mouth, and local application of cold lowers its temperature, both of which results might have been expected. But he also showed that merely holding in the mouth for two minutes, water, the temperature of which was the same as the initial temperature of the mouth (98·4° F.), is sufficient to raise the temperature of the mouth ·5° F., and that the effect is not increased if a stimulant to salivary secretion such as clove water is substituted for distilled water. Moreover, the duration of the rise of temperature in the mouth is very considerable, for both after holding water at 140° F. and water at 98·4° F. in the mouth, the temperature of the mouth is still found to be above its initial point three-quarters of an hour later. Conditions such as these preclude all possibility that the rise of temperature is merely of a physical nature, and it is difficult to understand, at least in the case of water at 98·4° F., any other afferent nerves as being concerned in the reflex act than those concerned with ordinary sensation.

### (iii.) Metabolic Changes associated with Normal Heat

**Production: The Respiratory Quotient.**—Since by far the greater number of the changes leading to heat formation are of an oxidative character, and since the amount of oxygen absorbed from the lungs is independent of the amount present in the atmosphere, and since this oxygen principally enters into combination with carbon and with hydrogen to form carbon dioxide and water, estimation of the amounts of oxygen taken up in respiration, and of carbon dioxide and water given off, afford valuable information concerning the oxidative processes going on in the body generally.

Now, though estimation of the amount of oxygen absorbed will not give any information concerning the amount of heat produced, unless we know whether it has been used in the oxidation of fat or of proteid or of carbohydrate, owing to the different heat values of these substances, and though the amount of expired carbon dioxide gives no information as to the kind of substance that has been broken up in its formation, the case is different with the "respiratory quotient," by which the ratio $\frac{\text{volume of } CO_2 \text{ excreted}}{\text{volume of } O_2 \text{ absorbed}}$ is commonly expressed. For the respiratory quotient is a relatively constant quantity in a normal animal upon a fixed diet, so that, if without any change in the diet the respiratory quotient of an animal undergoes change, information is given of a change in the metabolic processes going on in the animal itself.

Further, an indication is given as to the nature of the change in metabolic processes by the direction undergone by the respiratory quotient. For the respiratory quotient varies according to the diet upon which the animal is fed. If the diet be carbohydrate, the respiratory quotient is approximately 1, since in splitting up carbohydrate into $CO_2$ and $H_2O$, O is needed for combination with the C alone. Where, on the other hand, the diet is fat, besides such O as is needed to oxidise the C of the fat to $CO_2$ a certain amount of O is needed to supplement the O already present in the fat, in the formation of $H_2O$ from the H of the fat. Hence the volume of O absorbed is greater than where the diet is carbohydrate, and the respiratory quotient is less (·7).

With a proteid diet the value is about ·73, and with a mixed diet, such as that of man, about ·85. Consistently with the values given above, Pflüger found that the respiratory quotient of the herbivora is ·9–1·0, and that of the carnivora ·75–·80. According to Pflüger, the respiratory quotient is a highly stable quantity, and depends solely upon the metabolic processes going on in the animal, but this is denied by many authors of high repute (Vierordt, Voit, Zuntz, and others), who maintain that it may be altered by voluntary variation of rate and depth of respiration, and by muscular exertion. Nevertheless the value of the factor itself as an indicator of the *kind* of change that is going on in starvation or in fever, for example, cannot be gainsaid.

When first the subject of heat formation was investigated, it was held that the body heat is derived from destruction of proteid, but after the well-known experiment of Fick and Wislicenus the pendulum of opinion swung back, and it was the carbohydrates that were held responsible, such destruction of proteid as occurs being regarded as derived from direct tissue waste of the heat producing parts. At the present time it is held that the pendulum swung too far in this direction, for the fact that body heat can be maintained during starvation, and the fact that during the starvation the respiratory quotient sinks till it is equal to that of an animal on a pure proteid diet, show that if there be necessity proteids can be used as fuel. When, indeed, a starving animal has exhausted his store of carbohydrate and fat he falls back on his proteid. Thus Lehmann and Zuntz found that the respiratory quotient of a man undergoing a long voluntary fast was ·73 on the last day on which he took food, ·68 on the first day of the fast, ·65 on the second day, and constant at this point for the next 10–12 days.

But though the respiratory quotient is a relatively constant quantity, the factors of which it is composed are in the highest degree variable. With exercise the absorption of oxygen and the output of carbonic acid and water increase enormously. According to Speck, a marked increase of oxygen consumption occurs even with such slight movements as changing the position of the limbs, opening and shutting of the hands, etc.; of course with these same movements there goes an increased output of carbon dioxide. With exposure to a low external temperature both oxygen consumption and carbon dioxide output are increased, and to a degree that is approximately proportional to the lowering of external temperature. In small animals, such as the rabbit, guinea-pig, cat, this may be well marked in the complete absence of obvious muscular action, but in man, according to Löwy, no increase in metabolism takes place if shivering be prevented by a strong effort of will.

III. **Hyperthermia.**—It has already been mentioned in passing that there are limits beyond which on either side heat production and heat loss are powerless for the maintenance of a constant temperature; the temperature of an individual exposed to excessively high or excessively low temperatures for more than a very short time, rises or falls as the case may be.

Now, since we have placed the higher limit of temperature-variation compatible with normality in man at 37·8° C., it follows that temperatures above this should be regarded as pathological; but in some cases the symptoms accompanying such hyperthermia are so slight and so transient that they can hardly be removed from the category of physiological phenomena. Thus immersion in a bath at 44·6° C. (112° F.) for twelve minutes will raise the temperature of an individual (taken in the mouth) from 36·8° C. to 39·6° C. (98·2° F. to 103·2° F.) and will lead to faintness, palpitation, and rapid breathing, but though the temperature on leaving the bath is undoubtedly hyperthermic, the symptoms are those associated with a great exercise of the mechanisms presiding over heat loss, and, therefore, cannot with justice be called pathological. The hyperthermia, too, disappears or even gives place to a slight degree of hypothermia in about an hour, so that in spite of the great rise of bodily temperature the condition cannot be considered as over the border line separating physiology from pathology.

In the example given we have a case of hyperthermia due principally to diminution (temporary, it is true) in heat loss; production of heat is not increased excepting by the muscular action involved in increased respiration. At the same time, heat is directly added to the body from without, as the temperature of the bath is higher than that of the blood. Hyperthermia may also be produced if thermogenesis is increased beyond the counterbalancing powers of thermolysis; excessive muscular exertion, for example, can certainly raise the temperature of an individual, especially when external conditions are such that the possibility of compensatory thermolysis is at the same time diminished.

It is when all three conditions, increased thermogenesis, diminished possibility of thermolysis, and actual addition of heat to the body, are present, that hyperthermia is most marked, and there is then no doubt as to its pathological nature, since in not a few cases death of the patient occurs. Such are cases of insolation or heat-apoplexy.

(i.) **Hyperthermia from continued Exposure to High External Temperatures.**—The actual point to which the temperature of an animal can be raised without the supervention of death varies according to circumstances. Speaking generally, it is 5°–6° C. above the mean normal temperature (Cohnheim), but Rosenthal has shown the important and curious fact that a kind of active immunity to heat can be produced by repeated exposure of the animal to a temperature lower than that which would have been fatal had such an "immunisation" process not been undergone. Such previously prepared animals, when again exposed to a high temperature, show signs of heat retention, it is true, but those signs are much less marked, the temperature does not rise to so high a point, the respirations and the pulse are not so greatly accelerated, the general distress is less.

The temperature which the external medium must attain before signs of hyperthermia appear is profoundly modified by other conditions. Water is effective at a much lower temperature than air, air fully charged with moisture at a lower temperature than dry air, still air at a lower temperature than moving air. All these factors, of course, have bearings upon evaporation, and since evaporation is one of the most effective means for increasing heat loss, those conditions that hinder evaporation favour the occurrence of heat retention. A man who can remain in dry air at a temperature of 60°–70° C. for half an hour will probably not be able to remain the same length of time in a vapour bath, though the temperature is not above 45° C.; and in any case his body temperature on leaving the vapour bath will be higher than on leaving the hot air bath. Where muscular exertion has also to be undergone in a medium the temperature of which is high, symptoms of hyperthermia arise at a considerably lower external temperature. Thus workers in tunnels and in mines can hardly support a temperature of 40° C. however dry the air supplied to them may be; in the silver mines of Sierra Nevada, where the temperature is 42·2°–46·7° C., a man cannot work for longer than ten minutes.

The symptoms presented by a hyperthermic animal when its temperature is reaching a dangerous height are those of severe distress, respiration and pulse are accelerated, and the animal lies outstretched to present the greatest possible surface for loss of heat. If its temperature still rises, it becomes dull and heavy, even paralytic, the pupils are dilated, the pulse fluttering and hardly to be counted, and, immediately before death, convulsions may show themselves. The symptoms produced in sunstroke or heat-apoplexy are very similar; the face is red, pupils dilated, respiration increased, heart fluttering, the patient collapsed and delirious, his temperature raised perhaps to 44° C. (111° F.), and often death is preceded by convulsions. When it is remembered in addition that heatstroke especially affects individuals labouring in a hot, moist, and still atmosphere, such as soldiers marching in close order during the daytime in the tropics, stokers working in engine-rooms, hay-makers and harvesters, there can be no doubt that heat retention is the true cause of the condition. Though, even with copious sweating, hyperthermia cannot be prevented if the temperature of the external air be very high, the dangers of hyperthermia are much increased if sweating ceases, as it is likely to do unless fluid be drunk freely to replace the fluid lost by the skin. To this point reference will be made when discussing the Pathology of Collapse.

The cause of death in hyperthermia is somewhat uncertain.

Claude Bernard thought that death depends upon coagulation of the muscle-proteids, especially those of the heart; but this is probably not the case, as the coagulation temperatures of the chief muscle-proteids are higher than the temperature reached even in fatal hyperthermia (Halliburton). Moreover Laveran has shown that when the heart of an overheated dog has ceased to beat, contractions may reappear if the animal's thorax be opened in a cool room; it is hardly conceivable that this would be the case if the cause of cessation of heart's beat were coagulation of muscle-proteid. According to Ide, cessation of heart action must be attributed to alteration in the metabolism of the cardiac muscle and storage in it of injurious by-products, but this would not explain the phenomenon described by Laveran.

But though, if the hyperthermia be not too severe, death may not supervene, yet in man, as in lower animals, hyperthermia, especially if long continued, is followed by serious results. Indeed it is only in slight cases that perfect recovery occurs. Ill results follow, too, after the hyperthermia itself has disappeared; in man, cerebral symptoms of diverse nature, weakness of intellect and of body, are often seen after sunstroke, and in animals a progressive emaciation with ultimate death. How far these symptoms depend upon recognised anatomical lesions it is difficult to say, but in overheated animals marked fatty degeneration of cardiac and skeletal muscle, of hepatic and of renal epithelium is constantly seen. The actual effects of hyperthermia were investigated by Ziegler and Werhovsky. Rabbits were kept for periods varying between two and twenty-nine days in a chamber the temperature of which was 36°–40° C. After a few hours' sojourn in the chamber the body temperature of the animals was 2°–3° C. above normal. It was found that the most constant appearances were general wasting, diminution in the hæmoglobin content of the blood and in the number of red blood-corpuscles, moderate increase in the number of leucocytes, especially the large hyaline cells and the "polynuclear pseudo-eosinophil" cells (finely granular oxyphil cells), diminution in the number of lymphocytes. In the bone-marrow and the spleen there was found an enormous increase in amount of hæmosiderin and, later, fatty degeneration of the liver, kidney, and heart.

(ii.) **Hyperthermia from Cerebral Lesions.** — Besides hyperthermia from exposure to high external temperature, *i.e.*, heat retention due to insufficient heat loss, there is a variety of hyperthermia due apparently to increased heat production of cerebral origin unaccompanied by a corresponding heat loss. It has long been known that after compression or laceration of the cervical spinal cord in man the temperature of the patient may in certain cases be markedly raised, and similar results have been observed experimentally in rabbits and dogs. But it was not until after Wood, in an extensive series of experiments, had shown that in dogs a considerable rise of temperature takes place after division of the bulb from the pons, and after destruction of the first cerebral convolution, that the existence of a cerebral centre or centres presiding over the heat function began to be a subject of discussion. Wood's results have been confirmed and extended by a number of investigators, amongst whom Aronsohn and Sachs, Richet and Ott, and Hale White may be mentioned.

Aronsohn and Sachs showed that puncture into the corpus striatum produces a considerable rise of temperature, and that this rise is not due to injury of the superjacent grey or white matter. The rise of temperature being accompanied by an increased destruction of proteid, they conclude that the hyperthermia is due to increased heat production, a conclusion to which Wood and Ott, using the calorimeter, also come. Hale White, working on rabbits, found that the regions, injury of which lead to hyperthermia, are essentially the corpus striatum and the posterior portion of the cerebral cortex. Other regions, such as the septum lucidum and the crus, injury of which produce slight results, probably act by implicating fibres derived from the corpus striatum; the same is probably true also, according to Hale White, for the hyperthermia supervening after injury of the anterior end of the optic thalamus (Ott), for he finds that the rise is rarely greater than 1° F. With regard to the striate and the posterior cerebral regions, Hale White finds that injury leads to a difference in the characters of the hyperthermia;

whereas after injury to the corpus striatum the maximum temperature (about 3° F. above normal) is reached in 16½ hours after operation, and hyperthermia lasts 62½ hours, on an average, after injury to the posterior cortical region, the maximum temperature (which is less than that with striate lesions) is reached in 5 hours, and hyperthermia lasts 29½ hours.[1]

With regard to metabolism it is certain that the output of nitrogen is increased after injury of this description, but the respiratory exchange is probably unaltered; nevertheless on the latter point there is a divergence of opinion. In man, cerebral lesions, such as hæmorrhage and embolism, are accompanied at times by a rise of temperature, but this is more often seen, according to Dana, after hæmorrhage than after embolism or thrombosis. Such a rise of temperature is observed on the side opposite to that of the lesion, and has been shown to accompany lesions of the pons, of the corpus striatum, and of the cortex. Hale White in his Croonian Lectures showed the temperature charts of two persons suffering from hæmorrhage into the corpus striatum, in which the temperature in the axilla of the side opposite to the lesion was higher than that in the axilla on the same side; in one case the chart shows that such a difference persisted for four days, in the other for twelve days. Since in these same cases Hale White also found that the surface temperature and the secretion of sweat on the side opposite to the cerebral lesion were greater than on the same side, he concludes that heat loss was increased, and therefore that the higher temperature must have been due to increased heat production. This increased heat production was independent of muscular action (for the arm was paralysed), and was apparently independent of vaso-dilatation. Concerning the method whereby lesions such as those which have been described lead to increased temperature, we are completely ignorant, and it would not be profitable to enter into a discussion of the theories that have been put forward, especially as we are still uncertain whether vascular modifications can be completely excluded, and how far, therefore, we have to deal with a strict increase of heat production.

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[1] After a rise of temperature produced in this way has disappeared, a fresh rise may again be produced by a fresh puncture. This fact and the rapidity with which the rise of temperature appears, seem to preclude the possibility that the thermal change is of septic origin.

(iii.) **Hyperthermia following on the Administration of certain Drugs.**—It is known that a rise of temperature can be produced by the administration of certain drugs, but the method whereby these drugs act is in many cases highly uncertain. The rise of temperature seen after poisoning with strychnine may certainly in part be ascribed to the convulsions which characterise strychnine poisoning, but since the drug acts upon the nervous system, it is doubtful whether the increased production of heat in the muscles explains the whole rise of temperature. Belladonna and cocain, if given in large doses, also increase the temperature of the animal, but most important in this respect of all known drugs is $\beta$-tetrahydronaphthylamine, of which ·075 gm. given to a rabbit weighing 1600 gm. will raise its temperature 4° C. in one and a half hours and cause death (Stern). Since poisoning with $\beta$-tetrahydronaphthylamine does not lead to muscular activity, there is reason to believe that the drug directly influences heat production.

It is uncertain whether cases of high temperature seen in hysterical patients, of high temperature seen after passage of a catheter (" urethral fever "), of high temperature seen in different forms of anæmia, of high temperature seen in children during teething, slight disorders of digestion, etc., are to be associated with hyperthermia as it has been here described, or should be included along with fever. The characters of the high temperature in many of the cases given are different from those of fever, but not in all. Pembrey has found that the power of heat regulation at birth varies according to the state of development at which the young comes into the world; thus mice, rats, pigeons act almost like cold-blooded animals, whereas guinea-pigs and chickens, the development of which at birth is very advanced, react to changes in external temperature like warm-blooded animals from the first. From this it would seem that stability of heat regulation implies a relatively high degree of development, including therewith development of the nervous system, so that the hyperthermia of children and of hysterical patients, at least, may depend upon an instability or lower development of nervous system, evidences of which are also given in other directions by both classes of person. Whether we may with the necessary modifications apply such a suggestion to the hyperthermia of anæmia is another question, but there is no doubt that the nutritive condition of the nervous system in anæmia must be modified just as is the nutritive condition of the heart.

The remarkable elevation of temperature which is sometimes seen immediately before death, and which from this fact was termed " agonal " by Wunderlich, is partly of the hyperthermic and partly of the true febrile type. It must be looked upon as hyperthermic when it arises in the course of cerebral disease, such as epilepsy or cerebral hæmorrhage, but as febrile in such a disease as rheumatism or tubercular meningitis; for in the latter examples there is an exacerbation of the fever which is already present, whereas in the former examples " fever " as it is considered in the present work is absent, and the rise of temperature is an isolated phenomenon.

IV. **Hypothermia.**—Hypothermia may result from a variety of causes: from exposure to low external temperature, from starvation, from hæmorrhage, from the administration of various drugs, from injuries to the spinal cord; it may also occur as a constant associate of certain diseases and as a part of the states known as shock and collapse. The effects of hypothermia resulting from any of these causes are always of the same kind, however much they may, and do, differ in degree, just as the effects of hyperthermia are always of the same kind. These effects consist in coldness and pallor of the skin, sometimes combined with cyanosis of the extremities, in sluggishness of muscular action, whether voluntary or involuntary (thus respiration and cardiac action are slow, and the activity of the reflexes is diminished or abolished), in a tendency to drowsiness or in complete coma. These symptoms are the more marked the greater the degree of hypothermia, but a general sluggishness of nerve and of muscle in hypothermic persons and animals is always noticeable. It is hardly necessary to point out that this is in great contrast to the behaviour of the normothermic person when he feels cold.

(i.) **Hypothermia from continued Exposure to Low External Temperature.**—The normal animal when exposed to a low temperature diminishes heat loss and increases heat production, but if the external temperature be too low, or in particular if heat production be prevented, hypothermia results. A naked man cannot maintain his temperature in an external temperature below 27° C., and though many animals can well bear a lower external temperature than this, they cannot do so if they are prevented from setting in action the natural means of increasing heat production. The lowest rectal temperature compatible with life in man is not known, but Cohnheim speaks of drunken tramps picked up during the winter whose rectal temperatures were "30° C. to 26° C. or even 24° C."[1] For lower animals the minimal rectal temperature that can be survived, if especial care be taken in resuscitation, is 18° C. (Walther), but many of the cooled animals die even after they have regained their normal temperature. The rise of body temperature after cooling not uncommonly overshoots the mark, and the animal's temperature is then raised perhaps several degrees above normal; such animals become greatly emaciated and generally die. It is well in accordance with the general law that heat is a more effective agent than cold, that whereas a man can survive a fall in his temperature of 13° C. he can hardly survive a rise in his temperature of 6° C., and that the marked histological and functional lesions which follow on hyperthermia from exposure to abnormally high temperatures, are generally absent though a much greater degree of hypothermia has been produced by exposure to abnormally low temperatures.

(ii.) **Hypothermia in the Course of Disease.**—A persistently subnormal temperature is characteristic of certain chronic diseases. Of such diseases the various forms of nephritis and myxœdema are marked examples. Besides these, emphysema and some other forms of pulmonary disease, as well as many kinds of cardiac, and chronic nervous disease, are associated with a slight degree of hypothermia.

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[1] Page 1327, New Syd. Soc. Trans.

The degree of hypothermia in these cases is rarely great, but it is very constant. Usually the temperature oscillates about 36·7° C. (98° F.), being perhaps 37° in the evening and 36° in the morning, but it may be lower. With regard to myxœdema, a disease associated with atrophy of the thyroid body, Lorrain Smith has found that after removal of the thyroid body in cats, variations in external temperature have a greater effect on heat production than when the animals are normal. This would seem to suggest that in myxœdema it is the mechanisms presiding over heat loss that are at fault in determining the hypothermia, rather than those presiding over heat production. With regard to the causes of the hypothermia in the other chronic diseases mentioned above we are ignorant; probably they are not exactly the same in all cases.

In many acute diseases and in surgical injuries of a severe kind the temperature may undergo a sudden and marked diminution. This occurs in shock and collapse, conditions which, it will be seen later, are most commonly met with in surgical and medical affections of vital parts, particularly the abdominal viscera. Thus in acute generalised peritonitis from whatever cause, in severe injuries to abdominal organs, in hæmorrhage from a typhoid ulcer or from rupture of a tubal gestation, the patient's temperature will probably be found subnormal. It is not actually known upon what fault in heat regulation the hypothermia in these cases depends, but it is probable that heat production and heat loss are both deranged. Reference will again be made to this point.

In starvation the temperature is often very low, but one must distinguish between clinical "starvation" and experimental starvation or fasting. Experimental starvation, even though food is entirely withheld, is not accompanied by any great alteration in body temperature until starvation has been going on for perhaps three weeks and the animal is approaching death; we have in such a disease as carcinoma of the œsophagus a clinical example of a very similar condition. But in starvation, as a result of extreme poverty, the case is different, for the inability to purchase food implies an inability to purchase clothing, shelter, fuel, and, therefore, starvation in this sense implies starvation in the experimental sense *plus* exposure to cold. A starved person is therefore not only called upon to produce heat in the absence of food, but more than this, he is called upon to produce an additional amount of heat in order to counterbalance as far as possible the cooling brought about by exposure to external cold. This excessive demand cannot long be met, and starvation as a social experiment causes more rapid wasting, earlier fall of temperature, and earlier death from hypothermia than starvation as a pathological experiment. In starvation, after carbohydrates and fats present in the body have been consumed in heat production, the total heat production is derived from combustion of proteid.

(iii.) **Hypothermia from Administration of Drugs.**—Many drugs are known which lower temperature quite apart from the so-called "antipyretics" with which we are not at present concerned. Thus alcohol, chloroform, ether, morphia, chloral, curare when given in large doses produce a subnormal temperature. Hypothermia, too, is commonly seen after administration of poisons, whether vegetable (bacterial) or animal (snake), if the dose has been so large as to endanger life.

These drugs probably act in a variety of ways. Curare seems to lower temperature by interfering with heat production in the muscles; at least in a moderately curarised frog, heat production in the gastrocnemius, as evidenced by a resistance thermometer, is only found to occur so long as contraction follows stimulation of the sciatic nerve.[1] In a curarised dog or rabbit the heat production and respiratory exchange diminish by about one-third (Stewart). Nevertheless, the œdema which is so readily produced in a curarised dog or rabbit seems to show that some alteration of the blood-vessels has taken place, and therefore it is possible that increase of heat loss may also assist in producing the result.

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[1] See note, p. 428.

Alcohol, chloroform, ether, and chloral act by their effects on the vaso-motor centre and on metabolism; they lead to excessive dilatation of the peripheral blood-vessels, with the consequent increase of heat loss to which that peripheral dilatation of blood-vessels gives rise, and also lower metabolism. If these changes are combined with exposure to a low external temperature, hypothermia readily follows. A large proportion of those persons who are brought to hospital in a half-frozen condition in winter were drunk at the time of exposure to cold; the popular idea that alcohol "keeps out the cold" is a half-truth and a highly dangerous one.

The hypothermia which is often seen to a marked extent in cases of poisoning by acids and alkalies, *e.g.*, after poisoning with carbolic acid, must probably be referred more to shock produced by the extensive corrosion of throat and stomach than to the actual amount of poison absorbed. Shock also is no doubt largely accountable for the hypothermia accompanying severe cutaneous burns.

V. **Fever or Pyrexia.** — Fever, like inflammation, is a clinical term, and as such it is a name given to a group of symptoms. But it differs from inflammation in the fact that whereas it is generally agreed that no single phenomenon of inflammation can be described as "essential," in fever, on the other hand, it is generally agreed that a rise of body temperature is essential to the existence of the process.

Now, though a rise of temperature is essential to the existence of fever, every rise of temperature is not febrile. We have already described under the name "hyperthermia" a number of conditions in which the body temperature is raised, but in these fever in a strict sense is not present. The reasons for separating hyperthermia from pyrexia will be given later.

The symptoms which constitute fever, besides the rise of temperature, consist in alterations of cardiac and respiratory activity, functional and anatomical alterations in certain tissues, alterations in metabolism of a certain kind. Most of these changes are also found in hyperthermia, but a few are apparently peculiar to fever.

(i.) **Characters of the Temperature in Fever.**—A. **Classification of Febrile Temperatures.**—The classification of febrile temperatures usually adopted is that suggested by Wunderlich. According to it temperatures varying between 37° and 38° C. (98·6° and 100·4° F.) are described as "subfebrile"; between 38° and 38·5° C. (100·4° and 101·3° F.) as "slightly febrile"; between 38·5° and 39·5° C. (101·3° and 103·1° F.) as "moderately febrile"; between 39·5° and 40·5° C. (103·1° and 104·9° F.) as "pronouncedly febrile" or "highly febrile"; while temperatures above 40·5° C. (104·9° F.) are spoken of as "hyperpyrexial."

B. **The Stages of Fever.**—On examination of the temperature chart of a fever patient who has been kept under observation during the whole of his febrile attack, it will be found in the majority of cases that the curve can be roughly divided into three parts: (1) that in which the temperature was rising, (2) that in which the temperature maintained a high but fairly constant level, (3) that in which the temperature altered its characters, whether that alteration was in the direction of a fall or of a further rise. These stages are seen in every ordinary case of fever, and may be spoken of as (1) the initial stage, (2) the fastigium, and (3) the terminal stage.

(1) *The Initial Stage.*—In the initial stage of fever one has to distinguish between the internal and the superficial temperatures of the patient, for whereas the internal temperature rises, the superficial temperature most commonly is found to fall. A fall of superficial temperature, however, is not always observed, for if the initial stage be protracted the fall may be so small as to escape notice.

The initial stage is often marked by the occurrence of a rigor or fit of shivering, which gives the impression that the patient is cold. That he *feels* cold there is no doubt, and the experiments of Maragliano and of Geigel go far towards explaining his sensations. For Maragliano by means of the plethysmograph estimated the volume of the arm in a patient during the initial stage of an ague attack, and found that the volume of the arm decreased; this decrease must be ascribed to the presence in the arm of a smaller amount of blood than normal. Geigel's experiments are complementary to those of Maragliano, for Geigel showed that in the initial stage of fever, and particularly during rigor, the surface temperature falls. The diminished supply of blood (vaso-constriction) and the fall of surface temperature must therefore be correlated with one another. In accordance with the experiments of these authors one finds the skin cold and pale, perhaps cyanotic at the extremities, and the features pinched during the initial stage. The rigor itself is nothing more than a manifestation of the natural means for increasing heat production in answer to a sensation of superficial cold; in this connection it is important to note that in Maragliano's experiments diminution in volume of the arm commenced to show itself before the appearance of the rigor.

The internal temperature, on the other hand, in the initial stage of fever invariably rises, whether gradually, or by leaps and bounds. At first sight this might be supposed to depend upon heat retention from diminished heat loss, and no doubt this plays its part, but there is reason to believe that thermogenesis is actually increased, but whether apart from the increased heat production dependent upon the muscular contraction occurring during the rigor is another question. To this point reference will be made later.

(2) *The Fastigium.*—The second stage of fever follows immediately upon the first; in those cases in which there has been a well-marked rigor it commonly commences with the cessation of shivering. In this stage the internal temperature remains high, but the superficial temperature, so far from remaining low, rises very rapidly, and the skin soon yields to the touch that sense of pungent heat which is characteristic of fever. The internal temperature commonly shows some approximation to diurnal variations in that it is usually higher at night than in the morning, but these variations are

very irregular and uncertain. It is possible that the absence of regular diurnal variations, such as are seen in health, in part depends upon the fact that fever patients are confined to bed and are fed at very short intervals and through the night. Though the temperature is fairly constant during the fastigium, it is not absolutely so; slight exacerbations and remissions from time to time are very common. The duration of the fastigium is very variable; in malarial attacks it may not last more than an hour or two, in many of the acute fevers, *e.g.*, typhoid fever, it is prolonged for two or three weeks.

(3) *The Terminal Stage.*—The terminal stage of fever can, in some cases, be sharply separated from the fastigium, but in other cases such a distinction is hardly possible. This stage of fever presents different characters according as it is accompanied by ($\alpha$) a fall, or ($\beta$) a rise in the temperature.

($\alpha$) When the terminal stage is accompanied by a fall of temperature it is often termed the "stage of defervescence." The fall may be sudden or it may be protracted. When the fall is sudden the fever is said to end by "crisis," and when the fall is protracted, to end by "lysis." In crisis the temperature of a patient may fall perhaps from 40·5° C. to 36·1° C. (105° F. to 97° F.) in twelve hours, or the fall may take twenty-four or even thirty-six hours, but the fall is almost if not quite uninterrupted. In lysis, on the other hand, a normal temperature may not be reached for several days, and though during that time the general tendency of the temperature is downwards in that each night the temperature is lower than it was the preceding night, and each morning lower than on the preceding morning, yet the fall is not uninterrupted as in crisis, but there is an evening rise every day. In both crisis and lysis the temperature generally continues to fall somewhat after the normal has been reached, so that the patient's temperature becomes subnormal for a time before it becomes again permanently normal. This is more commonly seen in the case of a critical fall in temperature.

It is important in this connection to note that a fall of temperature in fever does not necessarily imply that the terminal stage has been reached, even though the fall may be as great and as rapid as it is in crisis. For sudden complications which supervene during the fastigium, and which are accompanied by shock or collapse, may lead to a marked fall in temperature owing to the diminished heat production and paralysis of the thermolytic mechanism by which those conditions are themselves accompanied. Thus, in typhoid fever, perforation of the intestine or hæmorrhage may occur during the latter part of the fastigium, and may cause the temperature of the patient to fall within a few hours from perhaps 40° C. to 36° C. (104° F. to 96·8° F.) or lower, and yet this is not a termination of the fever, still less a termination by crisis. It simply means that the temperature changes peculiar to shock or collapse have over-ridden and obscured those peculiar to the fever. The same is probably also true, though not so obvious, in many cases in which a febrile temperature gradually falls and death supervenes. Such a case is apparently one of defervescence by lysis, but since the disease itself shows no sign of retrogression, but rather of aggravation, in spite of the fall in temperature, we must probably regard the fall itself as a modification of the fastigium due to failing bodily powers and the consequent diminution of thermogenesis and paralysis of thermolysis, and not as a true terminal stage. This explanation derives support from the fact that in this case, as in the case of a pseudo-critical fall due to shock or collapse, the superficial congestion and profuse sweating, which are characteristic of the stage of defervescence, are almost always wanting; though a moribund patient may be covered with sweat, it is a "cold sweat."

($\beta$) When the fastigium passes into a stage in which the temperature is raised with greater or less rapidity and with greater or less regularity until death supervenes, it is common to speak of a termination of fever by hyperpyrexia and to consider the hyperpyrexial stage as a terminal stage comparable with the stage of defervescence by crisis or by lysis. This view is probably justifiable, for fever itself must be regarded as a special reaction of the heat mechanism to a definite stimulus, and if defervescence is cessation of the special heat reaction following cessation of the stimulus, the logical sequence of continued and increased action of the stimulus is continued and increased reaction of the heat mechanism, *i.e.*, hyperpyrexia. Practically and theoretically, therefore, hyperpyrexia must be regarded as the exact converse of defervescence. Indeed, were it not that the terms "crisis" and "lysis" are themselves bad, and were there in addition no etymological objections, one might even speak of "hyperpyrexia by crisis" and "hyperpyrexia by lysis," for the temperature may rise almost, if not quite, uninterruptedly until within a few hours it is 4°–5° C. above normal, or the rise may be interrupted and gradual and extend over several days.

The rise of temperature which we are now describing includes the truly febrile portion of Wunderlich's "agonal" elevation of temperature, in contradistinction to the hyperthermic portion which has already been mentioned (p. 439). Hyperpyrexial temperatures are rarely so high as hyperthermic temperatures, probably because a patient in whom hyperpyrexia supervenes is already weakened by the febrile disease, and succumbs to a heightened temperature more easily; the hyperthermic person, on the other hand, has generally been in a fair or good state of health previous to the rise of temperature. Hyperpyrexial temperatures of 41°–41·5° C. (105·8°–106·7° F.) are almost invariably fatal, but though in hyperthermia such temperatures are highly dangerous they are by no means necessarily fatal. Instances of recovery after sunstroke when the body temperature has reached 43° C. (109·4° F.) are not unknown.

(ii.) **Anatomical Changes in Fever.**—The effects of a febrile disease upon the system are a combination of the effects of the disease itself together with the effects of the high temperature which accompanies that disease. These effects are often very difficult to separate, and deductions as to the results of a febrile temperature are generally made from consideration of the results of hyperthermia. Such a course is hardly justifiable, since the causes of hyperthermia and of pyrexia are different, and since in all probability the processes concerned in the two forms of elevation of temperature are different also. Nevertheless some of the deductions made are probably correct.

The anatomical changes that can be ascribed to the action of a high febrile temperature itself are very few; the most evident is wasting, which affects not only the fat but also the proteid elements of the body. This wasting is to be correlated with certain metabolic changes that will be noted later. Another anatomical change very frequently seen in febrile disease affects the tongue. The tongue in disease has been carefully examined by Howship Dickinson, and he finds that the characteristic appearances of the tongue in various stages of acute disease are accompanied by variations in the amount of epithelium present. In a comparatively early stage of fever the epithelium is greatly increased in thickness, and this gives rise to the "coated" or "stippled" tongue; later, the amount of epithelium is still further increased, and the epithelium fills up the interspaces between the papillæ, giving rise to the "plastered" tongue; still later, this mass of epithelium peels off and yields the "red, denuded" tongue in which the papillæ are left bare and injected, or, if the patient is becoming convalescent, the epithelial mass is gradually softened by the saliva and removed from before backwards, leaving a "cleaning" tongue with a normal amount of young epithelium over the papillæ. Dickinson brings forward reasons for believing that this collection of epithelium on the tongue is due not only to deficient removal but also to increased proliferation. Though closely bound up with fever, this condition of the tongue is not solely dependent upon fever, for in about one-third of the number of cases in which the tongue was found to be coated, the temperature was normal or subnormal. Reference will be made below to the dryness of the tongue in fever.

To the fever itself one must probably also ascribe a part of the "cloudy swelling" which affects glandular and muscular cells, for cloudy swelling is more commonly seen in diseases that are accompanied by a high temperature than in those in which the temperature is low. Nevertheless, the fact that it is also found in infections where the disease has been accompanied by great prostration and a low temperature, seems to show that part of the change is independent of the pyrexia. Nor is the fact that hyperthermic elevation of temperature leads to fatty changes in the same tissues of great assistance, for the granules in cloudy swelling are not fatty. It is generally held, however, that the cloudy swelling of pyrexial disease and the fatty changes of hyperthermia are to be associated, and many authors hold that cloudy swelling is a transitional stage in the pathological conversion of proteid into fat. It is certainly in favour of this view that cloudy swelling is most commonly seen in rapidly fatal and acute pyrexial disorders, fatty changes in chronic pyrexial disorders.

Though hardly an anatomical change, we must probably also ascribe to the fever itself the oligoplasmia which, according to some authors, is frequently seen in febrile disease. Von Limbeck and Steindler found that the mean volume of the serum in the defibrinated blood of three non-febrile persons was 72·6 per cent., but that in eight highly febrile patients the mean volume of serum was only 54·8 per cent. Their results have, however, been referred by Biernacki to faulty methods.

An important change of the blood-plasma in fever is an alteration in its alkalinity. It has long been known that the blood in fever holds a smaller amount of carbonic acid than normal, and Minkowski found lactic acid in the blood of dogs in which fever had been experimentally induced. These factors must no doubt be associated with the diminished alkalinity which has been found to exist in many cases of fever. The amount of diminution varies considerably in different cases, but roughly speaking the amount of diminution is greater the more severe the disease; whether it stands in any definite relation to the height of the temperature is doubtful. The diminution in alkalinity persists after the fall of temperature in the terminal stage, and the normal level is only reached during convalescence; it is uninfluenced by any lowering of temperature brought about by antipyretic drugs. The cause of this change is quite unknown, though suggestions have been made that it depends upon altered tissue metabolism induced by fever, upon acid substances formed by micro-organisms, upon the formation of acid by-products during the disintegration of protoplasm that has been killed by bacterial toxins. But whatever the true explanation may be, it is probable that the change is highly important for the organism, for it is an unfavourable sign in febrile disease, and it is known that diminished alkalinity of the blood goes hand in hand with increased susceptibility to infection. In hyperthermia, whether caused by puncture of the corpus striatum or by exposure to high external temperature, the alkalinity of the blood is not diminished or is diminished to so slight a degree that it may be neglected.

Besides a diminution in alkalinity, an increase in alkalinity of the blood in fever has also been described. Biernacki indeed is inclined to consider that in man an increase is more common than a diminution in alkalinity. According to Löwit this increase of alkalinity is often seen in an early stage of febrile disease, though it may give place to a diminution in alkalinity later. According to Löwy and Richter the increase of alkalinity goes hand in hand with a diminution in the number of leucocytes in the blood, and can be brought out by a variety of substances which lead to hypo-leucocytosis, but this has been denied by other investigators. It is needless to point out that if we are to regard a diminution in alkalinity of the blood as important from the aspect of susceptibility, we must probably also regard an increase in alkalinity as important from the aspect of immunity. The coagulability of the blood in fever may either be increased or diminished, but enough has already been said in Chapter V. upon the subject of coagulation to render further remarks unnecessary here.

Changes in the number of red blood-corpuscles present in the blood during febrile disease are very common, but there appears to be no definite rule as to the direction taken by those changes; sometimes the number of corpuscles is normal, sometimes it is diminished, sometimes increased. But in spite of any intermediate variations that may have been undergone, the number of red blood-corpuscles decreases in cases of long continued fever. This seems to indicate that in fever there is a destruction of red blood-corpuscles, and, as will be seen later, the urine contains substances that can well be explained upon this supposition; but Naunyn and Minkowski have found that in rabbits and dogs, the temperature of which had been raised to 42° C. (107·6° F.) by keeping them in a warm chamber, the blood-serum shows no trace of dissolved hæmoglobin. In man, it is generally agreed that there is oligocythæmia in febrile disease, but the factors concerned are so numerous that it is hardly justifiable to ascribe the oligocythæmia to the fever alone, much less to ascribe it to destruction of corpuscles. Naunyn indeed considers that the differences in numbers of corpuscles depend more upon differences in the distribution of the blood in the body, and it is important to note that Breitenstein found in hyperthermic animals a marked diminution in the number of red blood-corpuscles present in the blood of the peripheral vessels, together with a marked increase in their number in the hepatic vessels. Nevertheless we are probably safe in saying that in febrile disease there is destruction of red blood-corpuscles. Changes in the numbers and characters of leucocytes have been already so fully described along with inflammation that they call for no further remark.

(iii.) **Functional Changes in Fever.**—Difficult as it is to separate the anatomical effects of fever itself from the effects of the disease which causes the fever, it is even more difficult, and in many cases it is at present quite impossible, to separate their effects upon function. The following are some examples of this difficulty. The disordered kidney function which leads to albuminuria is associated with cloudy swelling of the organ, and since we are unable as yet to decide how far the cloudy swelling is dependent upon pyrexia, how far dependent upon the cause of the disease, we cannot dogmatise concerning the function; probably, however, both factors are of importance. The increased rate of respiration seen in febrile disease may in part depend upon the overheated condition of the blood, for it has been found that if the blood supplied to the brain by the carotid is artificially heated, respirations are increased in frequency; but the mere mention of acute pneumonia is sufficient to show that the modification of respiration may depend upon alterations essentially due to the disease itself. The increased rate of heart beat may depend upon the fever, for heat increases the rate of heart's beat (Cyon), but it may also depend upon myocardial changes (such as those described by Scagliosi and others in diphtheria), or nervous changes brought about by the disease quite apart from the temperature. The nervous symptoms (delirium, stupor, coma, etc.) seem to be entirely dependent upon the rise of temperature, for along with the lowering of temperature which occurs when a hyperpyrexial patient is treated by the cold bath, there comes a surprising improvement in mental condition, which disappears if the temperature again rises after the patient has been removed from the bath. But as Cohnheim remarks,[1] "it is hard to say how much of this effect should be attributed to the cooling and how much to the improvement in the circulation and rise of blood-pressure, brought about by the bath." These examples are sufficient to show that it is impossible at present to discuss the effects of fever upon function if we use the term "fever" in a strict sense. In the following remarks, therefore, no such attempt will be made, and the changes in function described are those seen in febrile disease.

(*a*) *The Heart and Circulation.*—In febrile disease the rate of heart beat is increased and the pulse may be so rapid as to be impossible to count. According to the observations of Liebermeister the number of heart beats per minute rises by eight with every rise of 1° C. in the temperature (four and a half for every 1° F.), but though this "law" is roughly true it has many exceptions. With regard to the cause of this increased frequency of heart beat in fever, Frédéricq found that in febrile rabbits the rate of heart beat is not increased; since in the rabbit the vagus has no tonic action upon the heart, Frédéricq is inclined to refer febrile increase of heart beat to removal of cardio-inhibitory tone. With the increase of rate there also goes an alteration in duration of the systole and diastole; both of these are shortened but the diastole to a greater extent than the systole. Concerning the blood-pressure but little is known, and the statements that have been made are very conflicting. Towards the end of a febrile disease it is not unreasonable to expect that the blood-pressure would be low, and the running, weak pulse that is then present may probably be taken as a sign of a low blood-pressure. The condition of the blood-vessels themselves is modified in febrile disease, for a difference obtains between the reaction of the cutaneous blood-vessels to stimuli in health and in fever; thus slight cutaneous stimulation, *e.g.*, stroking with the finger-nail, will lead to a marked and widespread pallor lasting several minutes in a fever patient, whereas in a healthy person such a stimulus is almost without effect. Whether this difference depends upon local or upon central causes or upon both it is impossible to say, but that the blood-vessels are themselves altered in febrile disease is shown by the frequency with which petechial hæmorrhages are seen.

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[1] Page 1404, New Syd. Soc. Trans.

(*b*) *Respiration.*—Respiration in febrile patients is quickened, and the individual respirations are sometimes shallower, sometimes deeper than normal. The rate of respiration in fever is rarely so great as it is in hyperthermia. The normal ratio between rate of respiration and rate of heart beat (1 : 3–4) is generally maintained in fever, unless, as in the case of acute pneumonia, special conditions lead to a special rate of respiration. With an increase in the rate of respiration there is also a tendency for the extraordinary muscles of respiration to be brought into play; the dilatation of the alæ nasi with each inspiration in pneumonia is very characteristic.

(*c*) *Glandular Secretions.*—The glandular secretions are in many cases profoundly altered during febrile disease. The secretion of saliva is diminished and, as Dickinson has shown, placing upon the tongue a drop of dilute acetic acid, which normally leads to a profuse flow of saliva from Steno's duct, in febrile patients is followed by only a small flow or by no flow at all. A diminution in the amount of gastric juice secreted also occurs in fever, and it has been shown by many authors that such gastric juice as is secreted contains a smaller percentage of acid than normal; the amount of pepsin present seems to be less altered. Less bile than normal is secreted in fever, and its characters become altered; it becomes thick from the greater amount of mucus which it holds and darker in colour from the presence of a greater amount of bile pigment. It is probably to these alterations in the digestive secretions that the failure of appetite (anorexia) and the dyspepsia of fever patients are due. The mammary secretion in puerperal women attacked by any febrile process commonly diminishes or ceases entirely and the milk itself undergoes change, judging from the ill-effects produced upon an infant by feeding with the milk of a feverish mother.

The secretion of sweat in febrile patients shows marked differences according to the stage of fever under observation. In the initial stage it is greatly diminished if not entirely suppressed; during the fastigium it is sometimes diminished and sometimes increased, but in any case the skin itself during this stage is usually dry; sometimes the sweat collects beneath the surface of the skin and forms small vesicles known as "sudamina"; in the terminal stage, unless it be hyperpyrexial, sweating is enormously increased, and from this fact the terminal stage of fever has been called the "sweating" stage, a term that is still used in descriptions of an ague-fit. The occurrence of sweating in the terminal stage is best seen in those cases in which the temperature falls by crisis; the amount of fluid then secreted is often sufficient to saturate the blanket on which the patient lies. In defervescence by lysis sweating is not increased to so obvious an extent, but the general moisture of the skin, which is in marked contrast to the dryness obtaining during the fastigium, shows that the amount of secretion is increased. The statements made above are general only, for few exact measurements have been made upon the point: the chief are those upon which Hale White based the conclusions given in his Croonian Lectures. In hyperpyrexia there may be sweating, but a dry skin is far more common. The secretion of sweat in the terminal stage of fever was considered by Cohnheim to be dependent upon the vasodilatation which is also present in this stage, but it is more probable that the two phenomena are collateral results of a central modification than that the one is directly dependent upon the other; little was known concerning the hidrotic nerves at the time at which Cohnheim wrote. The characters of the sweat may at times undergo alteration as well as its quantity; in acute rheumatism, for example, it has a peculiarly sour smell and is highly acid.

The kidneys are probably not greatly altered so far as their functions are concerned, unless they are the seat of some anatomical change, and such alterations as undoubtedly appear in the urine are in all probability due rather to alterations in blood-pressure and in the blood presented to the kidneys than to differences in the way that the kidneys deal with that blood. In an ague-fit, which has a characteristic initial stage, fastigium, and critical defervescence, we find that the amount and characters of the urine vary in the different stages of the fever. In the initial stage there is an increased flow of pale but highly acid urine, which is of low specific gravity but which contains a greater amount of urea and of sodium chloride than normal; this increase in amount of urine must be regarded as, in part, dependent upon the increased blood-pressure that must result from the constriction of the cutaneous blood-vessels, and in part, as evidence of that correlation between skin function and renal function which is well known to exist. During the fastigium, in spite of the large quantities of fluid imbibed, the amount of urine is diminished, the specific gravity is increased, and the fluid is high-coloured and concentrated; this diminution must, in part at all events, be attributed to the greater amount of water lost by the lungs and skin in this stage. During the stage of defervescence the amount of urine is greatly diminished, its specific gravity is very high, it is high coloured, and it deposits large quantities of urates on cooling; this diminution must be correlated with the large quantity of water excreted by the sweat glands in this stage of the fever. These changes in amount of urine are fairly characteristic of all varieties of febrile disease, and it may be stated generally that during the initial stage more urine than normal is excreted, during the fastigium less than normal, and during defervescence much less than normal.

The meaning of the increased excretion of nitrogenous metabolites will be considered later, but certain of the other characteristics of febrile urine may be dealt with here. The fact that febrile urine usually contains a greater amount of potassium salts than normal (Salkowski) must almost with certainty be referred to the diminution in numbers of red blood-corpuscles that is known (at least in some cases) to take place in the blood. With this diminution in numbers of red blood-corpuscles must also be associated the high colour of febrile urine, though perhaps only in part, for there is reason to believe that the urinary pigments, both in health and in disease, are not exclusively derived from direct changes in blood-pigment. The sodium salts in febrile urine—unlike the potassium salts—are diminished, and in convalescence the contrast between the two kinds of alkaline salts is still maintained though in the opposite direction, for the excretion of potassium salts diminishes in convalescence, whereas the excretion of sodium salts increases. The chlorides of the urine are generally diminished in febrile disease; in pneumonia, for example, they may be almost completely wanting. The explanation of this fact is uncertain; Röhmann, finding that chlorides given in the food are not found either in fæces or in urine, concluded that they are retained within the body and enter into a somewhat stable composition with the proteids of the blood-plasma. Be this as it may, the amount of chlorides present in febrile blood is diminished, and with it the diminished excretion of chlorides by the kidneys must be bound up. Since the diminution in excretion of chlorides is noticed long before the sweating stage comes on, an explanation must not be looked for in this direction.

Besides the changes mentioned above, it is not uncommon to find small or sometimes large quantities of albumin (serum albumin and serum globulin) in the urine of febrile patients. In many cases this does not depend upon the fever as such but upon some change induced by the disease which leads to the fever; thus in tuberculosis of the lung we may have a highly febrile temperature and much albumin in the urine, but the presence of albumin will probably be due to lardaceous disease of the kidney. So also in scarlatina and diphtheria, the albumin often present in the urine is to be ascribed to kidney changes induced by the scarlatina or the diphtheria poison and not to the temperature. Albumoses are often found in the urine of patients in whom, from one cause or other, destruction of tissue is going on; thus it occurs during puerperal involution of the uterus, in patients convalescing from croupous pneumonia, in patients who are subjects of large abscesses, etc. Other alterations in the constituents of the urine have been described, but they can only be mentioned; acetone (also found in minute quantities in normal urine and in urine of persons suffering from cancer), diacetic acid (doubtfully present in normal urine), and oxybutyric acid (absent from normal urine) have been found in febrile urine; the sulphates are increased, and a larger amount of phosphorus is excreted than normal, a fact that is of importance in reference to the origin of the excess of nitrogen present in febrile urine.

Though the liver is the largest gland in the body, we are practically in complete ignorance as to the changes in its metabolism induced by fever. This ignorance is intelligible when we remember the experimental difficulties in the way of research upon the organ, and the doubt that still exists as to many of its functions even in health, but it is highly probable that investigation of the subject would bring to light facts of profound importance.

(*d*) *The Nervous System.*—With regard to the functions of the nervous system very little can be said more than that they are generally modified to a greater or less extent. The intellect is disordered, either being clouded or being abnormally active on abnormal lines, and hallucinations are not uncommon. When febrile disease has been prolonged, cutaneous reflexes may be abolished and involuntary evacuation or definite incontinence of urine and fæces may occur. The processes going on in the cardiac and vaso-motor centres are also abnormal, though no doubt the impulses discharged by these centres reach abnormal heart muscle and abnormal blood-vessel walls. Whether the injurious agent be the rise of temperature alone or the cause of the disease alone, or both combined, there is no doubt that the functions of the central nervous system are deranged in febrile disease.

(iv.) **The Metabolism in Fever.**—The metabolism in fever must be considered from the points of view of (*a*) the respiratory exchange, (*b*) the discharge of nitrogen.

(*a*) *The Respiratory Exchange.*—It has already been stated that though in fever the rate of respiration is increased, the depth of each inspiration may be increased or diminished; in any case, however, respiratory activity is increased. From the experiments of Löwy and of Kraus it has been shown that the intake of oxygen and the output of carbonic acid is increased during the initial stage of fever. This limitation of the period during which there is an increase in the intake of oxygen and output of carbonic acid (respiratory exchange) to the period during which the temperature of the patient is rising, is so strict that it has led Löwy to the belief that the increase of respiratory exchange is dependent solely upon the muscular contractions that occur during this period, especially if it be accompanied by a rigor. Though the carbonic acid and the oxygen are both increased, the respiratory quotient generally remains unaltered. During the later stages of fever the intake of oxygen and the output of carbonic acid are less than during the initial stage, and the respiratory quotient may remain constant or may fall somewhat, nevertheless none of these values are greater or less than they are for a healthy man on the same diet and under the same conditions as to muscular exertion.[1] So far as oxidative processes are concerned, therefore, the fevered and the non-fevered person do not differ except in respect of conditions implying an increase of muscular activity.

(*b*) *The Discharge of Nitrogen.*—The fact that in fever the output of nitrogen by the kidneys is equal to or even greater than in health was discovered by Traube in 1855. Since that time the subject has been investigated by many authors, and it may be stated generally that (1) the output of nitrogen in fever is far greater than it is for a healthy person on fever diet, and (2) the increase in nitrogen output begins before the temperature rises, is at its maximum at an early period of the fastigium, and, in those cases which end by crisis, often shows an epicritical increase. Now in the urine we obtain practically the whole of the nitrogen excreted by the body as the result of its metabolic processes, for loss by other ways is so small that it may be neglected; and since the nitrogen of the urine is only derived from proteid metabolism it follows that an increase in the amount of nitrogen present in the urine signifies an increase of proteid destruction in the body.[1] Hence examination of the urine of a fevered person teaches us that a greater destruction of proteid goes on in his body than in the body of a healthy person under similar conditions as to diet and exercise, a fact of which the weighing scales give evidence, for the fevered person wastes more rapidly than the starving person. Experimentally, the truth of this statement has been proved in the case of the rabbit by May, who found that the nitrogenous metabolism of the fevered rabbit is about 25 per cent. greater than that of the same animal in health and upon the same diet.

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[1] It must be remembered that the great rapidity of heart beat and of respiration in a fever patient imply greater muscular exertion, and consequently that his respiratory exchange must be expected to exceed somewhat that of a healthy person at rest even if the diets of both be exactly similar.

In health the nitrogen of the urine is divided amongst various substances; urea accounts for 84–87 per cent., ammonia salts for 2–5 per cent., uric acid for 1–3 per cent., and various extractives (xanthin bodies, kreatinin, etc.) account for 7–10 per cent. (Pflüger). These substances are all derived from disintegration of proteid, but so far as their origin is concerned they must be divided into two large groups: the urea group and the uric acid group. The urea group contains urea alone and is derived from proteid generally—apart from nucleo-proteids; the uric acid group contains uric acid, xanthin, hypoxanthin, sarkin, and other bodies closely allied to uric acid, and is usually regarded as being derived from nucleo-proteids.

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[1] Such an increase might depend upon removal of an amount previously stored in the tissues, and probably this accounts in part for the epicritical increase, but the statement made in the text is correct for all practical purposes.

The total amount of nitrogen excreted in members of the uric acid group bears a very constant relation to the amount of nitrogen excreted in urea, and hence we may conclude that there is normally a parallelism between the destruction of nucleo-proteids and of other proteids. But though the relative amount of nitrogen excreted in members of the uric acid group is practically constant, the absolute amount is very variable, and since the amount of uric acid itself excreted in health is very fairly constant, such variations in absolute amount must depend upon variations in the excretion of bodies belonging to the uric acid group other than uric acid itself (xanthin bases).

In fever the nitrogen derived from both sources is increased, but apart from complications the general relation between the excretion of the two groups is the same as in health ; certain modifications, however, are introduced. In the first place, the excretion of ammonia salts is increased not only absolutely but also relatively, and the increase takes place at the expense of the urea. In the second place, the greater amount of nitrogen excreted in members of the uric acid group almost entirely depends upon an increase in the amount of uric acid excretion: the excretion of xanthin bases is practically unaltered. This is exactly opposite to what obtains in health.

In fever, therefore, there is an excessive destruction of albumin and of nucleo-proteid, the former going to produce urea, the latter to produce uric acid. With regard to the origin of the uric acid, it is probable that it is derived in large part from disintegration of leucocytes, for Horbaczewski has shown that increase of uric acid excretion especially occurs when there is leucocytosis and breaking down of leucocytes. Moreover the increase of phosphorus in febrile urine, considered along with the large amount of phosphorus present in leucocytes, is suggestive in the same direction. Kühnau found in afebrile (leucocythæmia, malignant new-growths) as well as in febrile disease (croupous pneumonia, septic infection) that an increase in the number of leucocytes present in the blood is invariably followed by an increase in uric acid excretion, the maximum of which occurs when a previously existing leucocytosis disappears.

He also found that intra-peritoneal injection of material containing large quantities of leucocytes (aseptic pus, pounded thymus) leads to a great increase of uric acid in the urine. Kühnau's experiments are further important in showing that the excretion of uric acid does not seem to be dependent upon temperature, for the same result was obtained whether the patient was pyrexial or not. It is doubtful, however, whether destruction of leucocytes in fever is the sole cause of increased uric acid excretion, for cases have been described in which an increased uric acid excretion followed febrile conditions, unaccompanied by leucocytosis (Schnitzler); at all events it is not unreasonable to suppose that a portion of the uric acid may be derived from nuclei of tissue-cells destroyed during the febrile disease.

(v.) **The Ætiology of Fever.**—By far the greater number of diseases in which fever is a symptom are infective, and it is therefore natural to turn to the micro-organisms in endeavouring to discover the ætiology of fever. Amongst the micro-organisms, in this respect, animal as well as vegetable microbes are of importance, for of all the causes of fever the malarial parasites are perhaps the most important.

The relationship between micro-organisms and fever is particularly well shown in the case of intermittent fever (ague) and relapsing fever; for the rise of temperature in each disease coincides with the appearance of the micro-organism in the blood, the fever lasts as long as the micro-organism is present in the blood, and the temperature falls with the disappearance of the micro-organism from the blood. Whether in these cases the microbes act mechanically, or by virtue of poisons which they produce or by virtue of the direct changes to which they give rise in the blood and tissues, it is impossible to say. But in other cases there is no doubt that the micro-organism itself is not the cause of fever, at least mechanically; thus, in diphtheria there is fever, but the micro-organisms are, in the vast majority of cases, absent from the blood; moreover, fever can be induced by injection of diphtheria toxin apart from the micro-organisms altogether. Hence we must conclude that it is either the products of micro-organisms themselves, whether extra-cellular or intra-cellular, or else the products of the action of these substances upon the tissues of the animal that are the effective pyrexial agents.

Many experiments have been made with bacterial products, most of them being carried out by injection into the blood or the subcutaneous tissues of substances such as pus, infusion of putrid flesh, etc. Of these it is unnecessary to speak, as they were succeeded by others in which the nature of the substance injected was less complex, and consisted in the products of a single variety of micro-organism grown in an artificial medium. These experiments have taught that (1) substances causing a rise of temperature when injected into an animal may be produced by non-pathogenetic as well as by pathogenetic micro-organisms; (2) the pyrogenetic substance itself in such cases is usually an albumose.

But many other substances besides micro-organisms and their products lead to fever when injected into the circulation. Such are fresh and sterile extracts of muscle, thyroid, etc., fibrin ferment, commercial "peptones" (albumoses). Moreover, an "aseptic" fever is known in which a marked rise of temperature occurs after an aseptic injury, *e.g.*, fracture of a long bone. These facts (and others) have led Ughetti to reconsider the question, and finding that in all cases of fever there is evidence of blood destruction, he concludes that the true cause of fever is to be found in the hæmolysis. Ughetti's view is probably too narrow, but the fundamental principle underlying it, viz., that destruction of cells is to be associated with fever production, is probably correct. More than this cannot be said at the present time: What is the nature of the pyrogenetic substance? What is the method of its action? Have we to deal with one substance or many? are questions to which no answers can as yet be given.

(vi.) **Antipyretics.** — In 1882 and the succeeding years there was made known by Filehne a series of chemical substances which have the power of lowering febrile temperature. These substances, of which kairin and antipyrin are the most important, have a very marked and rapid action both upon man and lower animals. Their mode of action differs from that of the older antifebrile remedies such as quinine. Quinine, as for example in ague, lowers temperature by its action upon the micro-organism causing the disease, but kairin and antipyrin act by altering the condition of the blood-vessels in the skin and so increasing heat loss. The actions of kairin and antipyrin have been examined experimentally. Richter (kairin), working upon animals in which fever had been induced by injection of pyrogenetic substances, and Gottlieb (antipyrin), working upon animals made hyperthermic by cerebral puncture, showed by means of the calorimeter that thermolysis is increased. Maragliano (kairin and antipyrin), working with the arm-plethysmograph upon febrile patients, showed that the volume of the arm, *i.e.*, the amount of blood in the arm, is increased. Geigel (antipyrin), by his thermo-electric method, showed that surface temperature is increased before central temperature begins to fall. These facts are of course physiologically correlated, and hence we must conclude that kairin and antipyrin lower fever by acting on the central nervous mechanism which inhibits surface loss of heat.

Antipyrin and quinine diminish nitrogenous metabolism, but according to Kumagawa all other antipyretics, including kairin, increase nitrogenous metabolism. There is a marked difference between the action of antipyretics in health and in fever, for whereas in fever they lower temperature, in health they have no such effect. According to Richter, when the temperature of a febrile animal treated with kairin has fallen to normal, the surface loss of heat is diminished and actually falls below the normal. The importance of these facts will appear later.

(vii.) **The Theory of Fever.** — Having considered the principal characters of fever and the changes to which it gives rise in the body, it is now necessary to enquire into the theory of fever. The questions to which we shall endeavour, though with but partial success, to find answers are: (*a*) What is the nature of the febrile process? (*b*) What is the cause of the rise of temperature in fever? and (*c*) Why do we separate hyperthermia from pyrexia?

(*a*) *What is the Nature of the Febrile Process?*—It is only within the last half century or thereabouts that this question has been approached scientifically, and it dates its origin from the discovery that vascular processes are dominated by the nervous system. From the time when Virchow considered the subject and wrote his *Pathology* it has been customary to regard fever as a disorder of thermal regulation, though whether the disorder is primarily one of the central nervous system and secondarily one of metabolism, or primarily one of metabolism and secondarily one of the central nervous system, was a matter of doubt. On all hands it was agreed that there is a fever-exciting cause, but whether that cause attacks the nervous system and puts it out of gear with the result that metabolism suffers, or attacks the tissues, rendering them more labile than in health, with the result that the thermotaxic mechanism is thrown out of gear, was and still is a matter of doubt. Most authorities hold that the prime fault lies in the thermotaxic mechanism, but others, for example Ughetti, hold that tissue destruction by the fever-causing agent is primary.

Amongst those authorities who ascribe fever to a fault in the thermotaxic mechanism there is a great divergence of opinion. One school (that of Liebermeister, Filehne, Löwit, Richter, and others) maintains that the thermotaxic mechanism is abnormal, but nevertheless behaves approximately in the same way as the normal mechanism; the other school (that of Traube, Cohnheim, Senator, Krehl, and others) maintains that the thermotaxic mechanism is the same as in health but behaves in an abnormal fashion. The difference between these two views will become clearer as we proceed.

According to the Liebermeister school, in fever the thermotaxic centre is "set" for a higher point than it is in health. We can compare the idea with the "setting" of a thermo-regulator in the laboratory for a higher temperature. If such a thermo-regulator be set for (say) 20° C., directly the temperature of the fluid in which it is immersed falls below 20° C. the mercury in the regulator (taking this form of regulator as an example) contracts, with the result that more gas passes to the gas burner, more heat is given out, and the temperature of the fluid in which the regulator is placed rises; if, on the other hand, the temperature of the fluid rises above 20° C., the mercury expands, shuts off a certain amount of gas, the flame becomes smaller, and the temperature of the fluid in which the thermo-regulator is placed falls. Small variations occur on either side of 20°, but the temperature is kept constant, because a fall automatically invokes an increase in external supply of heat, and because a rise automatically invokes a diminution in external supply of heat. Now the thermo-regulator can be set at any temperature (say 30° C.) at will, and about that temperature the same series of changes will take place as have been described for a temperature of 20°. Liebermeister's view was that in fever the thermotaxic centre is set for say 40° C. instead of 37° C. and is therefore abnormal, but about the temperature of 40° the mechanism behaves approximately in the same way as normally it behaves about 37° C.

The phenomena upon which Liebermeister's view is founded may be exemplified in the following experiment. If a healthy person with temperature 37° C. be placed in a cold bath until his temperature has fallen about ·2° C. he shivers, if he be placed in a hot bath until his temperature has risen about ·2° C. he perspires. Exactly the same is true for a fever patient whose temperature is 40° C.; if he be placed in a cold bath until his temperature has fallen about ·2° C. he shivers, if he be placed in a warm bath until his temperature has risen about ·2° he perspires. But there is this difference between the two cases, the healthy man shivers at 36·8°, perspires at 37·2°, the fevered man shivers at 39·8°, perspires at 40·2°.

Now this behaviour both on the part of the normal and on the part of the fevered patient is so constant and so characteristic that it has attracted much attention, but it is a question whether the deductions that have been drawn from the experiment are justifiable. For it is doubtful whether the *central* temperature has anything to do with the phenomena at all, as is indeed suggested by the mere fact that one man shivers when his temperature is 3° C. higher than the other. It is surface temperature and not internal temperature that determines the shivering or the sweating. This is shown by the fact that if a healthy person whose internal temperature has been raised by placing him in a warm bath, and who is sweating, be suddenly and momentarily exposed to a draught of cold air, he shivers, and that not because his internal temperature has been brought down to below the normal, for it still remains above normal, but because a sudden fall has been induced in his surface temperature. In Liebermeister's experiments the cold bath certainly lowers internal temperature, but it first and to the greatest extent lowers surface temperature, the hot bath certainly raises internal temperature, but it first and to the greatest extent raises surface temperature. Hence the experiment shows that, in fever, the normal behaviour of the organism when its surface temperature is rising or is falling is not abolished, but it does not show that in fever the heat regulating centre is "set" for a higher temperature in the same sense as a thermo-regulator in the laboratory can be set for a higher temperature.

According to the Traube school the alteration of thermotaxis in fever consists in a derangement of that part of the mechanism which presides over heat loss. There is no question of "setting" for a higher temperature, but the higher temperature in fever is produced, in the initial stage, because heat loss is diminished owing to contraction of the peripheral blood-vessels, and in the fastigium because heat loss is diminished principally owing to the failure of evaporation from sweating. Upon the latter point, to which attention was first drawn by Leyden in 1868, great stress is laid, and there is no doubt that in fever the skin is commonly dry, but it has already been mentioned that this is not always the case. The fall of temperature in defervescence according to this school depends upon the greatly increased loss of heat brought about by the vascular dilatation and the profuse sweating that characterise this stage.

In spite of the fact that the Liebermeister school still claims some distinguished members, the views put forward by Traube, though not in their originally exclusive form, are rapidly gaining ground. Zuntz has shown that amongst reflex mechanisms that presiding over surface loss is the only one constantly in operation; Maragliano has shown that peripheral vascular contraction precedes the rise of temperature, peripheral vascular dilatation precedes the fall of temperature in fever; Giegel has shown that surface temperature is diminished and increased before the rise and the fall of febrile temperature, respectively, take place; Richter has shown that when the temperature of a febrile animal falls as the result of administration of kairin, the animal discharges more heat. All these facts indicate the importance of that portion of the thermo-regulatory mechanism which presides over heat loss in determining the processes of fever; but it must be remembered that this is not identical with an assertion that fever depends upon a derangement of the thermolytic function.

The suggestion has been put forward by MacAlister that in the brain we have three centres concerned with the heat function, a thermogenetic, a thermolytic, and a thermotaxic, and according to the one or other thrown out of gear so the characters of the temperature are modified. If the thermotaxic centre is deranged, then the temperature is irregular, if the thermogenetic or the thermolytic, then fever is produced; if all three centres are deranged, then we find an irregular rising febrile temperature. Upon this view the thermogenetic centre is in some way connected with the muscles, and the thermolytic centre with the blood-vessels, while the thermotaxic centre controls the other two.

There are many points which are left unexplained by MacAlister's hypothesis, such as the question whether the effect of cerebral puncture is to stimulate a centre presiding over heat formation or to paralyse a centre presiding over heat loss, both of which would produce the same result—a rise of temperature. Moreover, for the explanation of all variations of temperature, and the phenomena accompanying the maintenance of an even temperature in health, the existence of but one centre is theoretically necessary so long as it is constantly at work. The experiments of Zuntz have shown that the reflex mechanism for regulating loss of heat is always at work, and hence we need go no further than to imagine a centre presiding over thermolysis. The thermogenetic and thermotaxic centres of MacAlister are theoretically superfluous, though perhaps a definitely thermogenetic centre exists, judging from the effects of cerebral puncture. Derangement of the thermolytic centre must mean derangement of heat regulation, and so long as the centre acts at all, derangement of heat regulation must mean a rise of temperature, since production of heat is always potentially in excess of thermolysis. If the centre fails completely the case is different, for then no limitations are put upon heat loss, and the temperature is determined by heat production alone; complete failure occurs in shock, in collapse, in many persons during the last hours of life, and since under these conditions heat production is reduced to a very low level, we find that the temperature of such patients is correspondingly low. Nevertheless, MacAlister's suggestion is useful in that it suggests the possibility that definitely thermogenetic processes may play a part in fever, a possibility for which there are, as will be seen immediately, some very strong arguments.

The answer, therefore, to the question, What is the nature of the febrile process? with which we set out must be: It consists in the derangement of normal thermo-regulation, a process which is carried out in the central nervous system, and the most important part of which consists in regulation of heat loss; nevertheless abnormality in heat production undoubtedly plays a part also, though how great a part is at present undetermined.

(*b*) *What is the Cause of the Rise of Temperature in Fever?*— This question is closely allied with the one which has just been discussed, but the two are not identical. We may grant that the changes leading to fever are initiated in the central nervous system, we may allow that it is thermolysis which is essentially at fault, but that does not eliminate the possibility that the rise of temperature may be due to a disordered production of heat with which a disordered thermolytic mechanism is unable to cope.

Though a disordered thermolytic mechanism alone may account for a rise of temperature, it does not follow that a rise of temperature depends upon disordered thermolysis alone.

With regard to the cause of the rise of temperature in fever, the views of Liebermeister and of Traube were diametrically opposite. Liebermeister held that the temperature rises because there is a greater production of heat, Traube held that temperature rises because there is a diminished loss of heat.[1] Now, though there is no doubt that in the initial stage of fever the heat loss is diminished, there is equally no doubt that in a large number of cases during the fastigium the loss of heat is increased. This has been shown directly by Hale White from consideration of surface temperature and the amount of sweat secreted in a given time. Hale White found that in pneumonia and in erysipelas the heat loss is considerably increased, and since the temperature has risen he concludes that heat production must have been increased to an even greater extent. May, also, in the fevered rabbit found that the organism produces about 10 per cent. more heat than does the healthy animal upon the same diet, and the experiments of Nebelthau point in the same direction, though he finds a much smaller increase of heat production than May, and in a few cases found that heat production was practically normal.

It appears, then, that we cannot say that the rise of temperature in fever is due to diminished heat loss (heat retention) exclusively, or to increased heat production exclusively. Both heat production and heat loss are abnormal, and in one case it may be that the rise of temperature is due to an excessive heat production with which heat loss, though increased beyond the normal, is unable to cope, and in another case temperature may rise, though heat production is practically unaltered, because the diminution of heat loss is so great that heat is retained.

We have already considered heat loss at sufficient length, but heat production in fever must detain us for a moment. There is no difficulty in associating an increase of heat production in fever with the increase of nitrogenous metabolism; May found that in fever along with an increase of 10 per cent. in heat production there was an increase of 25 per cent. in nitrogenous metabolism above the normal. But when we ask whether this means that a central modification calls forth an increase of tissue metabolism in order to produce more heat, or means that the fever-exciting cause by its action on the tissues damages them and the heat is produced, so to speak, accidentally during the process of their removal, we can get no clear answer. Nevertheless, in febrile disease the tissues are undoubtedly damaged, and removal of the damaged tissue is necessary, and the leucocytes, to the destruction of which we have ascribed certain peculiarities of the nitrogenous metabolism, cannot be regarded as primarily directed towards heat production, so that it is perhaps easier (though one must not dogmatise upon the point) to adopt the second view, and hold that increased heat production in fever is, so to speak, accidental, and occurs only because the removal of damaged tissue-cells and leucocytes is carried out by a process of combustion.

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[1] Cohnheim held that both heat production and heat loss are modified in fever and that the rise of temperature depends upon both causes; Senator holds that modification of heat loss is alone responsible.

The fact that in certain cases there may be an increased destruction of proteid without a rise of temperature is only an apparent and not a real difficulty, for it need hardly be pointed out that increase of heat production and rise of temperature are not synonymous terms. It has been pointed out by Naunyn that in infective disease we may have increased destruction of proteid before the temperature rises; by von Noorden, that in malaria we may have increased excretion of urea, when, as the result of medication with quinine, the temperature does not rise; by Löwit, that in typhoid fever and septic infection we may have enormous destruction of proteid with but slight rise of temperature. But these facts do not mean that in the destruction of proteid no heat is set free, and that it is for this reason that the temperature does not rise: the failure to rise of the temperature under the circumstances must certainly be ascribed to a proportionate increase of heat loss, dependent probably in Naunyn's and in Löwit's cases upon a condition approaching to complete inactivity, and in von Noorden's case upon a condition approaching to normality of the thermolytic mechanism.

(*c*) *Why do we Separate Hyperthermia from Pyrexia?*—This question seems the more reasonable the closer the two conditions are examined. The temperature is raised in both, the respiratory exchange when the temperature is rising is increased in both, the nitrogenous metabolism is increased in both, the rates of respiration and of heart beat are increased in both, and anatomical changes of the tissues more or less alike are induced by both.

In a sense fever may be considered as a subdivision of hyperthermia, and at some future date it will perhaps be generally described as such, but at present it is advisable to keep the two conditions apart for the following reasons:—

1. The term "fever" is clinical, and is a useful term to cover a group of phenomena met with under a variety of circumstances and with the greatest frequency. Hyperthermia relatively to fever is a rare condition.

2. The causes of fever and of hyperthermia are absolutely different; this again is a clinical reason.

3. There are certain differences between the phenomena of fever and the phenomena of hyperthermia, notably the behaviour of the peripheral blood-vessels in the stage during which internal temperature is rising; the greater height to which the temperature can rise in hyperthermia without a necessarily fatal result; the shorter duration of hyperthermia (even after cerebral puncture it only lasts two or three days unless puncture is repeated); the frequency with which a rise in the alkalinity of the blood is seen in fever, whereas in hyperthermia the alkalinity either remains unaltered or sinks considerably; the different behaviour of animals made hyperthermic by cerebral puncture on exposure to external heat and cold as compared with the behaviour of fevered and normal animals.

When we have learnt to separate the phenomena of "fever" into those strictly due to rise of temperature and those strictly due to the cause of the disease of which fever is a symptom, the word "fever" will no longer have a meaning, but till then it may profitably be preserved.

(viii.) **The Meaning of Fever for the Economy.**—Just as we found in the case of inflammation that the process is considered by one school as purposeful and by another school as detrimental, so in the case of fever we find that some authorities ascribe to it a curative tendency, while others deny that it subserves any useful purpose whatever.

The idea that fever is beneficial is as old as Hippocrates, and down the centuries this view has at times been ascendant, at times the contrary view has prevailed. Hippocrates (430 B.C.), Asklepiades (100 B.C.), Rufus of Ephesus (100 B.C.), Sydenham (1650 A.D.), Hoffmann (1700 A.D.), all regarded fever as beneficial, but with Zacuto (1667 A.D.) there arose the opinion that it is an unqualified evil. Liebermeister held this view very strongly: "A man whose temperature is kept for some time at 40° or more succumbs of a certainty as the result of the increase of temperature; some die sooner, others later according to the individual resistance." Many pathologists and physicians followed Liebermeister, but Naunyn, Senator, Unverricht, and others held out on the opposite side. With the progress of bacteriology, the subject was again investigated, and now, experimentally. Walther investigated the effect of temperature upon rabbits infected with pneumonococcus; one animal was kept in a warm chamber at 40°–42° C., a control was kept at the room temperature. In five such experiments Walther found that the onset of general infection was prevented so long as the animals were hyperthermic, but as soon as they were removed from the warm chamber general infection set in, as in the control, and led to death. Rovighi, using the bacillus of rabbit septicæmia and anthrax bacilli, found that artificial warming prolonged, artificial cooling shortened life. Filehne, working with *Str. erysipelatis* on the rabbit's ear, came to similar results, with the addition that in the warmed animal the infection runs a more rapid, a more pronounced, and a more favourable course than in the cooled animal.

In the experiments of Walther, Rovighi, and Filehne, the animal was rendered hyperthermic by exposure to external warmth; Löwy and Richter investigated the question when the animal was rendered hyperthermic by cerebral puncture. It is impossible to deal with their important paper at length, but the general result of their experiments (made with pneumonococcus, swine erysipelas, chicken cholera, and diphtheria toxin) was to show that the increase of temperature exerts a decidedly beneficial effect upon the course of the disease. Thus with pneumonococcus they found in one case that the hyperthermic animal (temperature 41·1°) inoculated with a certain dose lived thirty hours, the control inoculated with only one-hundredth part of the dose died in twenty hours; in another case the control animal died in forty-eight hours, but the hyperthermic animal (temperature 41·5°), inoculated with four times the dose, survived.

Experiment, therefore, seems strongly to support the view that hyperthermia has a curative action, and thence it is but a short step to considering fever as beneficial, and as evidence of the setting in motion by the organism of one of its defensive mechanisms. And certainly in pneumonia, erysipelas, cerebrospinal meningitis, typhoid fever, the prognosis is better if the patient's temperature is moderately high than if it is definitely low. Nevertheless, Ziegler, consistent with his view as to the meaning of inflammation for the economy, holds that the rise of temperature in fever subserves no useful purpose but, as is shown by Werhovsky's experiments, produces changes that are unmitigatedly detrimental.

But even if we grant that fever is beneficial we are completely ignorant of the manner in which it acts. Whether it acts injuriously upon the bacteria or upon their toxins, whether it acts by virtue of the increased alkalinity of the blood which often accompanies fever, whether it increases the resistance of the tissues, it is at present impossible to decide. There are reasons for and against each of these suggestions.

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# CHAPTER XI.

## THE PATHOLOGY OF SHOCK AND COLLAPSE—TRANSFUSION.

*Synopsis.*

I. The Symptoms of Shock and Collapse.
II. The Causes of Shock and Collapse.
III. The Pathology of Shock.
IV. The Pathology of Collapse.
V. Transfusion.

SHOCK and collapse, like fever and inflammation, are clinical terms, and as such cover groups of symptoms. These groups of symptoms are, in the case of shock and collapse, very similar, but the pathological processes underlying the two conditions are different. Though one description of the patient's condition will therefore practically suffice for both, it will be necessary to discuss their pathology apart. By considering them in one chapter their points of resemblance and of contrast will be better brought out than they would be if each was relegated to the chapter with which, strictly speaking, it has most in common.

**I. The Symptoms of Shock and Collapse.**—When a patient is markedly the subject of shock or collapse he gives evidence of profound prostration. He lies perfectly quiet and in a semi-unconscious condition; if he can be roused it is only with difficulty and for a short time, yet during that time he answers questions clearly and rationally, though his voice may not be above a whisper. His appearance is changed; his face is pale and drawn, his lips and ears cyanotic, his eyes sunken, his cheeks hollow. His respiration is irregular and sighing, his skin cold and damp, his internal temperature often two or three, and sometimes five or six degrees Fahrenheit below normal. His heart-action is rapid and feeble, his pulse fluttering and weak, or, it may be, imperceptible at the wrist. His mouth and tongue are dry, and he experiences great thirst. Secretion of urine is diminished or there may be complete anuria. Nevertheless muscular power may not be so greatly diminished as other symptoms would suggest; a patient may walk to the hospital though suffering severely from shock, and though the condition which leads to shock proves fatal within a few hours. This comparative retention of muscular power is far more commonly seen in shock than in collapse.

II. **The Causes of Shock and Collapse.**—There is a great difference between the causes of shock and collapse, for in shock there can generally be determined a nervous element, whereas in collapse such an element is usually wanting. In this respect shock and syncope are closely allied, for just as intense emotions can cause syncope so they can cause shock. Nevertheless in shock some injury is generally added to the mental cause. This injury may be great, *e.g.*, laceration of abdominal organs in a "buffer" accident, or a severe burn, or it may be small, *e.g.*, a slight blow on the epigastrium.

Pain is undoubtedly a factor in the production of shock, for a greater degree of shock accompanies crushing of the highly sensitive finger than accompanies much more extensive injuries on the arm. But that pain is not the whole explanation is shown by the fact that, though shock has diminished to a large extent since the introduction of anæsthetics, it has not been abolished. Moreover, pain may be very great, as for example in tic douloureux or in toothache, and yet shock is absent. Nervous temperament, too, is apparently a factor. Cobbett relates the case of a nervous boy who, after removal of the tonsils (an operation so slight that it is commonly performed without the aid of an anæsthetic), remained semi-unconscious and almost pulseless for hours. In women generally, but especially in those who are of a highly imaginative nature (artists, musicians), the effects of pain combined with a nervous temperament in producing shock is often well-marked. If such persons be subjects of painful menstruation the onset of menstruation each month is not infrequently accompanied by signs of great, even alarming, prostration, which, however, passes off as the flow becomes established.

Profound shock accompanies injuries to the brain, whether those injuries are such as lead to macroscopic lesions, *e.g.*, hæmorrhage, laceration, or such as are summed up in the term "concussion." The first stage of concussion, in fact, is nothing more than a state of extreme shock, and the symptoms are practically identical with those given above with the addition that consciousness is more involved. Besides conditions affecting the brain, certain morbid conditions of the viscera are very liable to be associated with shock. Thus, the passage of a biliary or a renal calculus, perforation of the stomach or intestines, strangulation of a hernia, twisting of the pedicle of an ovarian cyst, rupture of the bladder or of an ectopic gestation, are fertile sources of shock. So also are the formation of a pneumothorax, even though, as in some cases of tuberculosis, the lung is so diseased that it is practically functionless, and the rupture of an aneurism, especially if it be of the dissecting variety.

From the examples given above it is clear that shock follows upon conditions suddenly produced and for the most part produced in comparatively healthy persons. In the majority of cases the patient is about his ordinary business when the accident, whatever its nature, arises. Shock then follows on rapidly, and the patient is found almost pulseless within a few minutes of the accident. If shock be severe and the patient's heart be examined immediately after the accident, complete absence of action may be found, but feeble pulsations commence within a short time. We have in this sudden onset of shock (which, it may be mentioned, does not always come on with such extreme suddenness as has been described above) a marked difference from the onset of collapse.

Collapse comes on more insidiously than shock, and it may take as many hours for collapse to produce the same degree of prostration as shock would produce in minutes. Moreover the person who becomes collapsed is, in a large majority of cases, already the subject of some disease; shock strikes a man down, collapse first attacks him when he is down. The chief causes of collapse are those which lead to a great loss of fluid from the body; such are profuse and prolonged diarrhœa or vomiting, profuse hæmorrhage, and probably also profuse sweating as in some cases of heat-stroke. Besides these, acute peritonitis of whatever origin is associated with profound collapse. Perhaps the most marked examples of collapse are met with in the "algid" stage of Asiatic cholera and in the diarrhœa of very young children. In the former case it is not even necessary that there should be diarrhœa, for though there may be no evacuation of intestinal contents, there collects in the bowel a large quantity of thin watery fluid, the so-called "rice-water stools." When diarrhœa is accompanied by vomiting, collapse makes its appearance much earlier.

Shock and collapse may be associated with one another, in which case the shock comes on first, and gradually merges into collapse. Unless it end in rapid death, as is not infrequently the case owing to the gravity of the injury which induces the shock, shock tends to recovery. Thus reference has already been made to the disappearance of alarming symptoms with the establishment of menstruation in highly sensitive women; and in simple uncomplicated concussion, the first stage—shock—is followed by stages in which the pulse becomes full and bounding, consciousness returns, and ultimately the patient recovers completely. But when, for example, a loop of intestine is lacerated by some injury and an intense peritonitis is set up by escape of intestinal contents into the peritoneal cavity, the ultimate condition of the patient is a mixed one, of which the shock is due to the primary injury of the intestine and the collapse is due to the peritonitis. The same association of shock with subsequent collapse is probably seen in a variety of conditions such as acute intestinal obstruction (especially when the obstruction is high up, for then the vomiting comes on earliest and is most persistent), twisting of the pedicle of an ovarian cyst, etc.

In the prostration following profuse and fairly rapid hæmorrhage we probably have collapse represented in its purest form and least complicated by shock. For when rupture of a blood-vessel leads to severe shock, hæmorrhage is, as a rule, comparatively trifling, partly because of mechanical obstruction to great output of blood, but more particularly because the shock of itself induces cardiac and vascular conditions incompatible with that maintenance of the blood-pressure which is, as we have already seen (p. 134), the chief factor in the persistence of hæmorrhage from a divided artery.

**III. The Pathology of Shock.**—It has been pointed out above that in shock we have evidence of a nervous element, whether that be central (emotion) or peripheral and reflex (pain, etc.). Moreover we have signs of marked cardiac and vascular disturbance. It has long been held that these are causally related, and that upon them shock is dependent.

It was shown by Goltz that if a smart blow be struck upon the abdomen of the frog, the heart is arrested in diastole, and the peripheral blood-vessels become dilated. Conditions such as these, it is unnecessary to say, must result in a fall of blood-pressure. Lowering of the blood-pressure can also be brought about in mammals by stimulation of the central end of the depressor nerve in the rabbit, and in not a few cases by stimulation of the central end of the divided vagus in the dog, the other vagus being intact. Hence there is no lack of evidence that centripetal impulses which reach the vaso-motor and the cardio-inhibitory centres can lead to a fall of blood-pressure. In the case of ordinary nerves of sensation, the evidence is not so clear, for stimulation of the central end of the divided sciatic in the dog usually leads to a rise of blood-pressure. But in most cases this rise of blood-pressure is temporary only, for if stimulation be continued the blood-pressure returns to its original level. Whether it ever falls below the original level as the result of prolonged stimulation of the sciatic nerve is uncertain.

The effects produced by these centripetal impulses are probably threefold: (1) they inhibit the vaso-motor centre and lead to an enormous dilatation of the smaller arteries, especially in the splanchnic area, and so to a fall of blood-pressure; (2) the dilatation of the splanchnic blood-vessels being brought about suddenly, it leads to so great a diminution in the intake of the heart that the heart receives little or no blood upon which to contract, with the result that cardiac action becomes slow and feeble; and (3) the centripetal impulses probably act directly upon the cardio-inhibitory centre, and lead to an arrest of heart-action.[1] Now in the case of mammals it is impossible to produce more than a temporary arrest of heart-action by stimulation of the peripheral end of the vagus nerve, owing to the appearance of idio-ventricular beats, and hence it is probable that though direct action upon the cardio-inhibitory centre may account for the cessation of heart-action which constitutes syncope (whether fatal or not), it does not account for the prolonged lowering of blood-pressure which is present in, and which constitutes the chief symptom of shock. Though, therefore, we cannot exclude the possibility that reflex inhibition of the heart may be concerned in the production of shock, we must regard it as being principally dependent upon a pronounced diminution of vascular tone which chiefly affects the blood-vessels of the splanchnic area, and which is induced by the action of afferent impulses whether of central or of peripheral origin upon the vaso-motor centre.

Once it is allowed that we have in extensive vascular dilatation brought about by reflex vaso-motor changes the true pathology of shock, an explanation of the symptoms observed in this condition becomes easy. For the lowered heart-action depends upon a diminution of the intake, and therefore a diminution of the output of the heart and perhaps upon direct cardiac inhibition; the failure of consciousness and the altered respiration depend upon an insufficient supply of blood to the brain and the respiratory centre respectively; the coldness of the skin and extremities upon the derivation of blood from them to the dilated splanchnic vessels; the fall of temperature upon inactivity of the thermolytic mechanisms combined with diminution of thermogenesis (whether brought about by inhibition of a definite thermogenetic centre or no, it is impossible to say); while the shrunken appearance of the face and the thirst are probably dependent upon dryness of the tissues, and are brought about by processes that will be discussed along with the pathology of collapse.

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[1] It is generally accepted that in mammals, as in the frog, arrest of the heart can be brought about by reflex stimulation of the cardio-inhibitory centre. This is probably true, judging from clinical evidence, but experimentally, I have never seen cardiac arrest brought about by stimulation of the central end of an afferent nerve. Even stimulation of the central end of the divided vagus (the other nerve being intact), though it often slows the heart and leads to a considerable fall of blood-pressure, has never in my experience led to complete arrest of heart-action. I have performed the experiment some dozens of times upon dogs and rabbits.

There is one condition which is frequently seen in shock, to which reference has not yet been made. It was noticed by John Hunter over a century ago, while bleeding a patient, that the blood which issued from the vein was bright red. Since the blood-flow at this time was slow, Hunter argued that the arterial hue could not depend upon a more rapid flow of the blood through the capillaries. Brown-Séquard investigated the condition and came to the conclusion that the peculiarity depends upon an "inhibition of exchange," by which he meant that the vital processes which normally bring about a removal of oxygen from the blood, and a giving up of carbonic acid to the blood, are suspended. According to Brown-Séquard, the essential factor of "nervous shock" lies in this inhibition of exchange, and he supported his view by recalling the fact that, in shock, drugs, etc., introduced into the stomach or into the subcutaneous tissue are not absorbed, and do not produce their physiological action during the period of shock, but are first absorbed when shock is passing off.

Roger has supported Brown-Séquard's view, and will not allow that shock depends upon vascular paralysis; according to this author the arteries are often constricted. He found that when the head of a frog has been crushed, strychnine, injected into the abdominal vein, fails to produce its physiological action. This fact, he suggests, can be explained either on the hypothesis that the tissues are unable to react, which is improbable, or upon the hypothesis that the poison does not pass from the blood to the tissues, which is probable if for "the tissues" we read "the spinal cord." Contejean made the objection to Roger's experiment that the method of producing shock injures the blood-supply of the cord so greatly that there is no evidence that the strychnine ever reached the cord at all. He, himself, found that if in a frog prepared by Roger's method strychnine be injected into the central end of the abdominal aorta after ligature of the two aortic branches, tetanic symptoms ensue. Moreover, in this tetanic frog, which, having been prepared by Roger's method, should, according to that author, be the subject of shock, it is still possible to induce shock, for violent crushing of the head inhibits the spinal cord and puts an end to tetanic convulsions.

Roger replied to Contejean's criticisms by showing that crushing of the head is not necessary for the production of shock, but that when it follows the discharge of a Leyden jar over the lumbar region (in which case there is no interference with the circulation in the cord), the action of strychnine is suspended for a time. Moreover, he showed that veratrin, which prolongs the period of contraction of voluntary muscle in the normal animal, does not produce any effect in a frog treated after the manner described. He sums up his view of shock by describing it as "a collection of phenomena resulting from a violent excitation of the nervous system which is characterised by a series of inhibitory acts, of which one only, the inhibition of exchange, is constant and indispensable." In this country, however, the view set forth previously is the one commonly accepted, with the addition that the reflex inhibition is considered to act upon "all the functions of the nervous system and is not limited to the heart and vessels only" (Mansell Moullin).

IV. **The Pathology of Collapse.**—It has already been pointed out that collapse accompanies diseases in which the body loses large quantities of fluid, and that when vomiting is persistent, collapse comes on earlier and is more pronounced. These facts strongly suggest that loss of fluid is the true cause of collapse, a suggestion which has been raised to a certainty by the experiments of Roy and Cobbett.

The post-mortem appearances presented by a person who has died of Asiatic cholera, in which, as has already been said, collapse is often extreme, are very remarkable. The intestines are full of a watery fluid, the spleen, liver, and lungs are tough and leathery, very little blood is present in the body, and such as is present is so viscid that it has been said to resemble tar. The state of the blood is not due to post-mortem change, for the same condition has been observed during life. These appearances point to the conclusion that the fluid which has collected in the intestines has been derived from the viscera. In the case of collapse following abdominal operation and in peritonitis it is true that these appearances are not seen after death, though the aspect of the patient and the vomiting which generally accompanies peritonitis are compatible with a general decrease of the amount of fluid in the solid tissues. The experiments of Roy and Cobbett have, however, shown that under these conditions the solid tissues and the blood do lose water, and that the water which they give up collects in the injured tissues.

Sherrington and Copeman to some extent anticipated Roy and Cobbett in reference to the subject of collapse (though they speak of the condition as "shock"), for they found that when the abdomen is opened along the linea alba, especially if the abdominal contents are disturbed, the specific gravity of the blood rises. Roy and Cobbett, using dogs, opened the abdomen widely, disturbed the intestines, and, as a rule, divided them between ligatures in several places. The experiments lasted often from twelve to eighteen hours, and during that time frequent observations were made upon the specific gravity of the blood, of voluntary muscle, and of the intestinal wall, while throughout the experiment a continuous graphic record was kept of the blood-pressure in the carotid. They found that the specific gravity of the blood for the first hour or two after opening the abdomen undergoes no change, but that the specific gravity of voluntary muscle increases, and the specific gravity of the intestinal wall diminishes to a marked extent. Later, the rise in specific gravity of muscle comes almost to an end, and then the specific gravity of the blood begins to rise; the specific gravity of the intestinal wall continues to fall. For some hours after the specific gravity of the blood has begun to rise, the blood-pressure shows no sign of falling, but the pulse becomes smaller and more rapid; when at last the blood-pressure begins definitely to fall, it falls rather rapidly, and death usually occurs a few hours later. The temperature of the animals shows a marked tendency to fall, but loss of heat was obviated in the actual experiments by keeping the animal suspended over a bath of warm water.

The explanation of these phenomena is given in the words used by Cobbett in his article on "Shock and Collapse" in Allbutt's *System of Medicine.*

"The events which occurred in these experiments as the result of a severe abdominal operation may be arranged in three periods:—

"(*a*) During the first period fluid was poured out into the injured tissues; but the blood remained unaffected by this loss, because an equal quantity of fluid was passing into it from the uninjured tissues.

"(*b*) During the second period this compensatory flow of fluid became insufficient to meet the loss, the density of the blood gradually increased and signs of failure of the circulation began to appear; nevertheless the arterial pressure remained practically unchanged.

"(*c*) The third period was that of the fall of blood-pressure, and it continued until the death of the animal.

"The duration of the first period varied in different cases from one to several hours. It probably depended partly upon the severity and extent of the injury, and partly upon the quantity of fluid present in the tissues of the animal at the beginning of the experiment."

It was calculated that during one of these experiments the blood may lose as much as one-third of its original volume, and since, for a certain number of hours before it began to increase in density, fluid was leaving the tissues, the total amount of fluid that must have been abstracted from the body generally to collect in the region of injury must have been enormous.

The experiments of Roy and Cobbett are completely in harmony with those made by the author upon the pathology of œdema and described in Chapter VI.

In human beings Grünbaum has also observed a rise in specific gravity of the blood under similar conditions. Cobbett refers to three cases of laparotomy in which Grünbaum found that the specific gravity of the blood rose from five to seven points. In dogs Roy and Cobbett found a rise in specific gravity of as much as fourteen points, but the conditions were of course exceptional.

The pathology of collapse, therefore, consists essentially in an abstraction of water from the solid tissues and the blood.

In the case of burns and scalds it is probable that the prostration so commonly observed is in part caused by shock, in part by collapse. We can hardly refuse a part to shock if we bear in mind the great degree to which cutaneous sensory nerves are concerned in these conditions, but that collapse also plays a part is shown by the experiments of Sherrington. Sherrington found that though the animal be under the influence of an anæsthetic at the time of the experiment, and though the nerves be cut to prevent subsequent pain, immersion of the hind limbs in hot water leads to a marked rise in the specific gravity of the blood which may last for two or three days. It is highly probable that along with increase in density of the blood there goes an increase in density of the solid tissues, and these, together with the output of fluid in the injured region, present a condition exactly comparable with that in the experiments of Roy and Cobbett.

Now the effects which, when produced on a large scale, lead to collapse, take place on a small scale when the experimental interference is so slight that it does not lead to shock or collapse. This is shown by certain experiments made by the author. If the two hind limbs of a dog be tightly bandaged from below upwards so as to render them completely anæmic, and after an hour (the reason for the delay will appear subsequently) the specific gravity of the blood and of the solid tissues (voluntary muscle) be taken and the bandage be removed, it will be found that in a short time the specific gravity of the blood has fallen somewhat, and the specific gravity of the solid tissues has risen considerably. The explanation of these facts obviously is that when the capacity of the vascular system is suddenly increased, fluid enters the blood from the tissues to increase the volume of the blood. In this case, however, there is at most only a slight output of fluid into the tissues of the previously bandaged limbs, and therefore the specific gravity of the blood shows a definite fall instead of remaining constant as it did in Roy's and Cobbett's experiments where the injury to the tissues was great, and where the output of fluid into them was great also.

It is probable that this drying and consequent shrinkage of the tissues explains in part the shrunken features seen in shock and collapse, for in collapse there is no doubt that the specific gravity of the solid tissues rises, and in shock the conditions produced by a sudden dilatation of vessels in the splanchnic area is exactly comparable to the conditions produced in the experiment just mentioned when the bandages are removed from the hind limbs. Nevertheless the shrunken features must in part be due to the fact that both in shock and in collapse the peripheral blood-vessels are contracted.

V. **Transfusion.**—A large number of cases in which prostration occurs are so obviously associated with conditions in which a considerable quantity of blood (hæmorrhage) or of other fluid (Asiatic cholera) has been lost by the body, that, naturally, replacement of fluid was early thought of as the means whereby the prostration was to be met. Without going into the clinical aspect of transfusion it may be said that the fluids used have chiefly been defibrinated blood and salt solution. Though the reasoning upon which transfusion was undertaken was sound, the practice has fallen into a considerable degree of disrepute, partly owing to the dangers accompanying transfusion (especially if blood is used), and partly because relief, if obtained, was only temporary. In this section the experimental side of transfusion will be discussed and an endeavour will be made to account for the evanescence of relief given by transfusion to the patient. In the author's opinion there is a great future for transfusion as a therapeutic means in cases of collapse and probably also in some cases of shock, but the mode in which transfusion is to be carried out in order to obtain lasting relief must be different from that which has hitherto been adopted, and must conform with indications received from experimental pathology.

The volume of fluid which may experimentally be injected into the circulation of a dog through the external jugular vein without raising the arterial blood-pressure for more than a very short time is surprising. It is possible thus to inject an amount of saline solution or of blood equal to one-half or two-thirds of the original volume of blood without producing the slightest discomfort to the animal or any permanent rise in its aortic blood-pressure. It is true that while the actual injection of fluid is proceeding the aortic blood-pressure, as measured by a manometer in the carotid, rises, but this is due to the fact that the amount of blood reaching the right heart during each diastole is temporarily increased by the amount of fluid injected, and therefore the output of the left ventricle is temporarily increased also; but directly the injection of fluid ceases the arterial blood-pressure begins to fall and very soon again[1] reaches its original level. This behaviour of the blood-pressure, however, is only seen when its level before the injection was at or about the normal. If the blood-pressure previous to injection was low, as for example after division of the cervical spinal cord or division of the splanchnic nerves, a full return to the original level after the termination of injection does not take place, but on the contrary the blood-pressure is permanently left at a higher level than obtained before injection. The difference varies according to the amount of fluid injected. This distinction is one of great importance in connection with transfusion in cases of shock and collapse.

Now maintenance of the blood-pressure under the first set of conditions mentioned, so far as the vascular system is concerned, can only be brought about by an increase in the capacity of the vascular system; for if the capacity of the system remained the same and the volume of fluid within it were increased the pressure within the system must rise.

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[1] Within a minute; if the injection be carried out slowly, even this temporary rise is absent and the tracing yielded by the arterial blood-pressure maintains a constant mean level throughout.

The capacity of the vascular system may be increased in three ways, either by an active dilatation of the small arterioles, or by a passive (or active) distension of the capillaries and veins, or by both. It has been shown by Roy and Adami that in the dog intra-vascular injection of a small quantity of defibrinated blood may double the output of the heart, and we have already seen that increase in output of the heart raises the blood-pressure, unless it be accompanied by a corresponding diminution of peripheral resistance, so that since the blood-pressure in a transfusion experiment remains constant it follows that the peripheral resistance must be diminished. The small arterioles in the body must be dilated, and the increased vascularity of superficial parts after a copious intra-vascular injection shows that this is the case. But if the amount of fluid injected be equal to one-half or two-thirds of the original volume of blood, dilatation of the arterioles alone would be insufficient to prevent a rise of blood-pressure. Here the distensibility of the veins comes into play. The veins generally, but in particular those of the splanchnic area, become dilated, and it is in this portion of the vascular system that the main increase of capacity takes place. The blood-pressure in the large veins in such a case does not rise, and this is, of course, due to the fact that, though the small veins contain more blood than normal, they are more dilated. Whether the venous dilatation is brought about in an active manner through the control of nerves, or whether it is that they are passively distended because the arterial dilatation exposes them to a greater proportion of the force exerted by the ventricle, it is impossible to say: in some more or less modified form the latter view is the one that is usually held.

But though large intra-vascular injections are in the normal animal practically without effect upon the blood-pressure, it is impossible to believe for a moment that they are completely without influence upon the body. Cohnheim, it is true, found on injecting enormous quantities of saline solution into the circulation that the glands which normally secrete a watery fluid, *e.g.*, kidney, salivary glands, commence to pour out their secretions in large quantities. But it is easy to show that even small variations in the amount of fluid in the blood-vessels have their effect. In the last section mention was made of the modifications in specific gravity undergone by blood and muscle on removal of a bandage. The first part of the experiment was not mentioned, but it is highly instructive from the point of view of transfusion. When one or more limbs of a dog are rendered completely bloodless by tight bandaging from the paw upwards with an elastic bandage a new set of conditions is introduced. The body, so far as the circulation is concerned, consists of the animal *minus* the bandaged limb into which no blood can enter, and since in this "diminished body" there circulates the same amount of fluid as circulated in the whole body previous to the application of the elastic bandage, the "diminished body" is in the same position as if a certain volume of fluid had been directly injected into the circulation and the limb had not been bandaged. One important difference, however, must be noted: by this method of producing plethora the disadvantage of injecting a fluid which differs from the blood in some greater or less extent is entirely avoided, for the fluid whereby the plethora is produced is absolutely normal to the animal in composition.

The effects of plethora induced after this manner[1] are marked, though they are not to be looked for in modifications of blood-pressure or in secretion of urine or saliva, or in any other of those points which were recognised by Cohnheim. About an hour after the establishment of plethora it is found that the specific gravity of the blood has risen, the specific gravity of the tissues as represented by voluntary muscle has fallen. Fluid of lower specific gravity than the blood has therefore left the blood, fluid of lower specific gravity than the muscle has entered the muscle. Moreover, on centrifugalising specimens of blood and comparing the ratio borne by the volume of the plasma to the whole blood, it is seen that after plethora has been established the volume of the plasma diminishes. Nevertheless it is not plasma as such which leaves the blood-vessels but something less than plasma, for it is found that the specific gravity of the blood-plasma has risen. When, therefore, the ratio between volume of blood and capacity of blood-vessels is suddenly disturbed by a sudden increase in the volume of the blood, the normal ratio is in a short time re-established by the aid of a transference of a portion of the blood-plasma to the voluntary muscles. The length of time that it takes for this re-establishment of equilibrium is very short, the whole process is complete in an hour at the most, and the new levels of specific gravity are maintained until other processes have reduced the specific gravity of the blood and raised the specific gravity of the muscles to what may be spoken of as the normal levels. This latter portion of the process, however, is far more gradual.

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[1] Plethora induced in this manner is sometimes known as "plethora apocoptica."

Now though the effects of removing the bandage upon the specific gravity of blood and of tissues are identical in direction, though, of course, not identical in degree, with the effects of copious hæmorrhage, certain important and instructive facts appear when the volume of the blood is increased by actual injection of fluid, which do not appear or are not clearly seen in plethora apocoptica. The fluid which is used for injection is, in the vast majority of cases, "normal saline solution," which has a specific gravity of 1005. As a result of its admixture with the blood the specific gravity of the blood falls to a greater or less extent according to the amount of saline solution injected. The lowest point of specific gravity is reached almost during the very time of injection, and from the moment when injection ceases the specific gravity of the blood begins to recover itself. The rapidity with which it does this, *i.e.*, the rapidity with which fluid is transferred from blood-vessels to the tissues, depends essentially upon the amount of fluid which the tissues already contain. If the animal have been deprived of water for twenty-four hours before the experiment, the rise in specific gravity of the blood is more rapid than if the animal have been plentifully supplied with water; in summer the rise is more rapid than in winter, and so on. The first portion, too, of any given return to normal is more rapid than the later portion, so that if, for example, the specific gravity of the blood rises ten degrees in the hour subsequent to injection, eight of those degrees will have been accomplished during, perhaps, the first half-hour.

But the amount of fluid which the tissues can hold is limited, and the fact that this recovery of specific gravity by the blood after intra-venous injection depends upon the amount of fluid in the tissues, is well seen by making a series of copious intra-vascular injections in the same animal at intervals. If, in a dog weighing 13 kilos., 300 c.c. of saline solution be injected into the circulation, the blood will be found to have recovered completely from an initial fall in specific gravity of perhaps ten degrees in about one hour, but if a second intra-vascular injection of the same amount be now given, the specific gravity of the blood will not recover itself completely under about two hours, while after a fourth or fifth injection the specific gravity of the blood may remain at its lowest point (and this is lower than after any of the previous injections), without more than a bare attempt at rising, for hours. The tissues show corresponding changes in specific gravity: after a first intra-vascular injection the voluntary muscles fall in specific gravity to a greater extent than they do after a second or a third, while if a series of intra-vascular injections be given, it will be found that a point is reached when the muscles undergo no further change in specific gravity at all. It is when this condition of the muscles obtains that the specific gravity of the blood remains close to its lowest point for hours. The tissues, therefore, may be regarded as a reservoir, by variations in the contents of which the volume of the blood is kept constant.

But there is yet one more fact that is demonstrated with the utmost clearness by copious intra-vascular injections of saline solution, and it is that after a first and perhaps a second injection of a series the specific gravity of the blood not only recovers itself completely after its initial fall, *but goes beyond the* *mark.* There is absolutely no doubt that if a copious injection of salt solution has lowered the specific gravity of the blood from, say, 1064 to 1054, the specific gravity of the blood will rise from 1054 and continue to rise until it has passed the original specific gravity of the blood and reached perhaps 1066 or 1067. Further, the result of a second intra-vascular injection may be of two kinds. Continuing the example just given, the rise from the initial fall in specific gravity after the second injection may be complete when the specific gravity of the blood is 1065 (higher than the initial specific gravity of the blood but lower than the specific gravity of the blood immediately before the second injection was given), or it may continue to rise until it has reached 1068 (higher than before either the first or the second injection). It is one of the most astonishing paradoxes of experimental pathology that the specific gravity of the blood can actually be raised by injecting into it a large quantity of a fluid having a considerably lower specific gravity than itself.

Now these experiments teach most conclusively that if transfusion is to be used as a therapeutic means to combat shock and collapse, a single injection of fluid is worse than useless. For in shock and in the later stages of collapse the blood-pressure is low, and if the maintenance of a moderately high (normal) blood-pressure is the object to be attained, it cannot be attained by a single injection unless the quantity of fluid introduced is appalling to the surgeon. And if, as is more likely, the drying of the tissues and the inspissation of the blood is the evil to be overcome (at least in collapse), a single transfusion is equally futile. For in collapse, and probably also to some degree in shock, the amount of fluid in the tissues is greatly diminished, and it has been pointed out that, when an animal has been deprived of water, the specific gravity of the blood falls less as the result of intra-vascular injection, regains the original level in a shorter time, and overshoots the mark to a greater extent. The results, therefore, that have been gained by practical experience are exactly those which experimental pathology would have us learn.

But it is important to note that as the tissues become saturated with fluid this tendency of the specific gravity of the blood to overshoot the mark diminishes, and after a third, fourth or fifth injection, injection of a fluid of lower specific gravity than the blood leads to a prolonged and marked lowering in the specific gravity of the blood. It is quite possible that the discredit attaching to transfusion as a therapeutic means is simply due to the fact that transfusion has not been given a fair trial. To allow it a fair chance of success it should be repeated again and again at short intervals until it has produced a marked and more or less permanent effect upon the specific gravity of the blood.

In the normal animal the specific gravity of the blood can also be lowered (and its volume at the same time increased) for a short time, by injection into the circulation of a concentrated solution of a crystalloid. This diminution of specific gravity takes place in a surprisingly short time. Thus if, in a dog weighing 13 kilos., 18 gms. of glucose dissolved in 30 c.c. of water be injected into the jugular vein, it will be found two or three minutes later that the specific gravity of the blood has fallen perhaps ten degrees, and the specific gravity of the blood-plasma perhaps four degrees. Such diminutions in specific gravity indicate that the volume of the blood has been increased by perhaps one quarter.

Sherrington and Copeman have found that the diminution in specific gravity of the blood brought about by injection of strong sugar solution lasts longer than that brought about by weak saline solutions, and it has been suggested (Cobbett) that a plan of treatment dependent upon transfusing strong sugar solutions "offers some prospect of success." Since the fall in specific gravity of the blood brought about by injection of strong solutions of crystalloids depends upon an abstraction of water from the tissues, it seems to the author that not much assistance can be expected in this direction, partly because the amount of water in the tissues has already suffered a severe diminution, and partly because a further diminution would probably only aggravate matters. Nevertheless it is likely that better results would be obtained if, instead of a "normal" sodium chloride solution, a weak solution of glucose (say 2·25 per cent.) were used in transfusion, for glucose is better borne by an animal than sodium chloride. The author has frequently seen small intra-vascular injections of an 18 per cent. solution of sodium chloride prove fatal to a dog, whereas he has never found intra-vascular injection of a 55 per cent. solution of glucose produce the slightest symptom that might cause alarm. Solutions of these strengths are no doubt excessive, but their use shows that in transfusion less risk is run if glucose is injected than if sodium chloride is injected, a point which is important in connection with the repeated transfusion that has been advocated above as a therapeutic measure.

It will have been noticed that in the preceding pages no mention has been made either of sudden diminution in abdominal or thoracic pressure or of poisons as causes of shock and collapse. The effects of both of these are often very similar to those of shock and collapse, but in the case of poisons at all events (whether bacterial or non-bacterial), we are so ignorant of their method of action that it is at present impossible to decide whether they cause shock or collapse, or indeed whether they cause either of these conditions as they have been described above. It is possible, however, that with advancing knowledge the effects of many poisons may be shown to depend either upon vascular paralysis (shock) or upon inspissation of the blood (collapse).

In the case of sudden diminution of abdominal pressure (as, for example, in paracentesis) the pathology of the faintness which may occur, and which by many clinicians would be spoken of as "shock," is quite different. The diminution of pressure leads, it is true, to a withdrawal of the blood from the rest of the body to the implicated region, but the nervous element which is characteristic of shock is quite absent. The dilatation of blood-vessels (*cf.* p. 131) is brought about by mechanical and not by reflex nervous causes. If anything, the patient's general condition probably *approaches* more to collapse than to shock, for one would expect the sudden increase in capacity of the vascular system, like the removal of the elastic bandage from the limbs of the dog in the experiment already described, to lead to a rise in specific gravity of the tissues and a fall in specific gravity of the blood. But of this we have no direct evidence, and even if it be true, the actual condition would not be one of collapse, since the very changes which are characteristic of collapse, and upon which the collapsed condition depends, would be those which, in the case of paracentesis and allied conditions, would bring about amelioration of the symptoms. For where paracentesis is needed the tissues are commonly waterlogged, and transference of fluid from them to the blood-vessels must be rather an advantage than otherwise. Probably the symptoms sometimes seen after paracentesis, etc., are due solely to a cerebral anæmia suddenly brought about by mechanical causes and quickly rectified.

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# CHAPTER XII.

## The Pathology of Nutrition.

*Synopsis.*

- I. General Considerations on Nutrition.
  - (i) The Blood-Supply.
  - (ii) The Cell.
  - (iii) Influence of Nervous System.
- II. Local Death.
  - (i) Gangrene.
  - (ii) Coagulation-Necrosis.
  - (iii) Colliquative-Necrosis.
  - (iv) Fat-Necrosis.
- III. The Degenerations and Infiltrations.
  - (i) Fatty Changes.
  - (ii) The Lardaceous Change.
  - (iii) Colloid, Mucoid, and Hyaline Changes.
  - (iv) Cloudy Swelling.
  - (v) Calcification.
  - (vi) Pigmentation.
- IV. Atrophy and Hypertrophy.
  - (i) Atrophy.
  - (ii) Hypertrophy.
  - (iii) Fibrosis and certain Allied Changes in Bones and Joints.
- V. The New-Growths or Neoplasms.
  - (i) Definition.
  - (ii) Classifications.
  - (iii) Histological Characters.
  - (iv) Nutritional Changes undergone by Neoplasms.
  - (v) Pathogenesis.
  - (vi) Cysts.

The pathology of "nutrition" is logically co-extensive with pathology, for every pathological condition is fundamentally a nutritive one. But it is customary to restrict the meaning of the term to certain changes seen in the tissues. These are: local death; the degenerations and infiltrations; atrophy and hypertrophy; and the formation of new-growths. To this custom we shall adhere, and after a few remarks have been made on the pathology of nutrition generally, we shall discuss the above subjects in the order given.

I. **General Considerations.**—Since the tissues are composed of cells or their derivatives, nutrition of a tissue comes to mean nutrition of its component cells or cell-derivatives.

These cells take up substances from the blood or lymph, build them more or less closely into their own structure, break some of them down in the performance of function and cast the waste products again into the lymph. Hence normal nutrition depends upon two factors, the blood and the cell. When either of these is abnormal, nutrition is altered, and with the alteration of nutrition there come modification of structure and modification of function. Nevertheless it does not follow that we are always able to detect the structural alteration with the means at our disposal, for greater changes are necessary to produce recognisable structural alteration of cells than are necessary to produce recognisable functional alteration.

The blood and the cell are themselves subject to many influences. The blood is constantly changing in composition; food, drink, substances thrown into it by other cells, whether for removal from the body or as internal secretions, all produce their effect. The cell possesses an inherent power to feed itself which it has received from its parent, and in the majority of cases it is under the control of the nervous system. The action and inter-action of blood and cells must therefore bring about that inter-dependence of tissues to which reference was made in the first chapter, and no alteration of nutrition in one part can be without its effect upon the nutrition of all parts. We must therefore consider briefly in connection with the pathology of nutrition, (i.) the blood-supply, (ii.) the tissue, (iii.) the influence of the nervous system.

(i.) **The Blood-Supply.**—As we have already dealt fully with the blood and circulation, it is unnecessary to consider this factor in nutrition at length. From what has been said, it is clear that all conditions which modify the constitution of the blood or its distribution are liable to produce tissue-change. In most cases the blood-supply or the blood itself is altered in the direction of deficiency. The heart is enfeebled, the blood-vessels are narrowed or obstructed, there is oligocythæmia or oligochromæmia, or the blood-plasma is more watery than normal or fails to contain some internal secretion. Sometimes the direction is in that of excess, but since the tissues themselves are a determining factor in their own nutrition, an excessive supply of blood acting alone must be very marked and long continued before it produces tissue-change, except in the case of delicate tissues such as nerve-matter and gland. Sometimes the blood contains a completely abnormal substance, as in the case of poisons, whether inorganic (*e.g.*, phosphorus, arsenic) or bacterial (*e.g.*, diphtheria toxin, etc.), or a substance which is normally discharged from the body (*e.g.*, in uræmia).

Modifications of the blood also produce modifications of the lymph. But the lymph may also undergo changes on its own part; the chief of these consists in absorption of abnormal substances from the tissues, *e.g.*, bacteria and their toxins, pigments, portions of malignant new-growths, etc. Deposition of these in lymph-glands leads to alteration of nutrition and tissue-change, here and elsewhere.

(ii.) **The Tissues.**—The tissue-cells possess an inherent power of taking up nourishment from the blood, which they inherit from their parent cells, and which is independent of the nervous system. This is seen well in the case of the leucocyte; it lives, moves, takes up solids and liquids into itself, and reproduces itself, independently of the nervous system and of the blood-supply, only needing that a nutrient fluid shall be presented to it. It is especially true of the most important of all cells—the sperm and germ cells—and is probably true of all cells in the body. The same inherited power to take up nutriment from the blood is also found in the cells of a sarcoma or carcinoma, for these grow and reproduce themselves in characteristic fashion quite apart from nervous system and quite apart from function.

Where, then, there is an inherited fault in the power of taking up nutriment from the blood, there must be impaired nutrition[1] and a corresponding tendency to tissue-change. One of the faults probably has reference to the longevity of the cell, and this might well account for pathological conditions in which tissues and cells undergo senile changes at an early period of somatic life. So, too, an inherited fault in power of the cells to take up nourishment from the blood may underlie many of the diseases in which a hereditary tendency is recognisable.

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[1] In their work on hereditary transmission of acquired immunity, Charrin and Gley found that the offspring of rabbits that had been actively immunised with bacilli or toxin (*B. pyocyaneus*) were considerably below the normal weight even 6–8 months after birth. Charrin and Nobécour carried the question further and studied the daily growth of infants over long periods. They found that whereas the lowest daily increase of weight was 16 gms. in the case of children born of

But besides this inherent power, cells are physiologically stimulated to the intake of nutriment by exercise of their function. In this they are largely aided by changes in the blood-supply, for it is a law that functional activity is accompanied by an increased supply of blood. But increased vascularity probably does not afford a complete explanation, for we have seen (p. 123) that when functional necessity is in abeyance, increased vascularity alone does not lead to an increased output of lymph.

Disuse is one of the most important causes of impaired nutrition and tissue-change. Thus the ductus arteriosus at birth, the thymus gland after the first year of life, the uterus after parturition, the lower jaw after the teeth have been removed, have all of them entirely or largely lost their function, and partly as a result of this fact their nutrition fails and they undergo tissue-changes. The muscles, too, that normally move a joint, undergo changes and ultimately show great wasting if, from disease, that joint becomes immovable.

(iii.) **The Influence of the Nervous System upon Nutrition.**—At the end of Chapter VII. (p. 288) the question was discussed whether the nervous system plays a part in determining the course of an inflammation, and it was said that on the whole it is probable that the nervous system exerts a direct influence on the process. That it exerts an *indirect* influence on inflammation is certain. In the case of nutrition generally we are in a somewhat stronger position. There is no doubt whatever that a nerve-cell exercises a nutritive influence upon

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healthy parents, when one or both parents were diseased, increases of 0, 2, 4, 5, 9, 11 gms. per diem were often observed. The infants were all suckled by wet-nurses.

its particular axis-cylinder, for the axon degenerates when it is separated from its proper ganglion cell. There is no doubt, too, in infantile paralysis (acute anterior poliomyelitis), a disease characterised by atrophy of the large multipolar cells in the anterior horns of the cord, that the wasting of muscle is due not only to disuse, but also to the loss of a physiological stimulus normally passing from these ganglion cells to the muscles which they control. That such a stimulus normally exists is shown by the experiments of Mott and Sherrington. These observers found that if the posterior roots of the lumbo-sacral or of the cervico-brachial plexus be divided on the proximal side of the ganglion, though the limb is not moved by the animal (even after the lapse of months) and undergoes a wasting from disuse, yet it still can be caused to contract by stimulation of the appropriate cortical area or of its efferent nerves for months after the operation; moreover, it apparently undergoes no degeneration. If, on the other hand, the anterior roots be divided, the muscles degenerate rapidly, and no such results from stimulation of the efferent nerves can be obtained after a very short time. The perforating ulcer of the toe occurring in tabes dorsalis, the acute bed-sores seen in some cases of apoplectic hemiplegia, the cutaneous eruptions that sometimes trace out with wonderful accuracy the course of a nerve and its branches (herpes zoster), and some other conditions, are strong evidence of the same nervous influence upon nutrition. Nevertheless this mass of evidence must not be regarded as proving the existence of distinct "trophic nerves"; the existence of special nerve-fibres controlling the nutrition of tissues is very problematical. But whatever view be taken of the existence of trophic nerves, it is certain that disturbance of normal innervation directly modifies the nutrition of skin and lowers its power of resistance to microbic invasion.

II. **Local Death.**—We have already pointed out in connection with inflammation (Chapter VIII. p. 328) that persistence of irritant action is a cause of gangrene and allied conditions. But though inflammation and the changes accompanying inflammation constitute one of the most important causes of local death, they are not the only causes. We must therefore consider local death from a more general point of view.

Local death is a concomitant of somatic life, for death of cells goes on side by side with reproduction and growth of cells in every tissue. But in this case the general structure of the tissue does not change, and the whole process is physiological. With this kind of local death we have no concern. The kind of local death that interests us from a pathological point of view is death involving masses of cells. The number of cells involved is at times so small as only to be discoverable with difficulty and by aid of the microscope, at times so great as to involve a whole member. We shall consider (i.) gangrene, (ii.) coagulation-necrosis, (iii.) colliquative-necrosis, (iv.) fat-necrosis.

(i.) **Gangrene.**—Two varieties of gangrene are known: (*a*) dry gangrene or mummification, (*b*) moist gangrene or sphacelus.

The differences between these forms of gangrene are differences of moisture and of putrefaction. Dry gangrene only occurs when rapid evaporation takes place from the dead material. It is therefore found especially when the part is exposed to the air, when the epidermis which opposes evaporation is removed, when death of the part has been brought about by cutting off its arterial blood-supply. A typical example of this variety of local death occurs in the shrivelling of the umbilical cord after birth. In this case the umbilical vessels no longer convey blood, the cord, instead of being surrounded by a liquid medium (amniotic fluid), is surrounded by air, and therefore the conditions are such as to favour drying. Dry gangrene also occurs in cases of arteritis deformans (" senile gangrene ") and, generally, in all conditions, pathological or surgical, in which an artery is occluded and collateral circulation is not established.

Moist gangrene occurs under the opposite conditions, viz., when evaporation is hindered and when blood reaches the dying part or cannot escape from the vessels of the dead part. Hence moist gangrene occurs in tissues which have mortified as the result of extreme venous obstruction or of intense inflammation, and in parts which, in addition, are still covered with epidermis.

Moist gangrene shows a marked difference from dry gangrene in respect of putrefaction, for since moisture is necessary to the growth of micro-organisms, a dead part which contains a considerable amount of water as well as a large amount of albuminous material is an eminently suitable nutrient medium for bacteria, and putrefactive varieties grow in it with readiness. These putrefactive bacteria and the enzymes which they produce break up the constituents of the dead tissue, with the result that nuclei disappear, the outline of cells is lost and the soft tissue becomes converted into a pulpy mass. These changes, of course, occur sooner the more cellular the tissue, where it is resistant (bone, tendon, fibrous tissue), anatomical appearances remain for a much longer time; indeed, in the case of bone, which contains practically neither proteid nor water, there is little difference in appearance between the living and the dead. As a final result, the gangrenous mass comes to contain leucin and tyrosin, crystals of ammonio-magnesium phosphate, crystals of margaric acid. At the same time, the iron of the disintegrated blood-pigment, which has escaped into the tissues generally from the blood-vessels, is converted into a sulphide by the sulphuretted hydrogen liberated from the decomposing proteid, and gives to the part a greenish-black colour. The liberated gases of putrefaction cause a part undergoing moist gangrene to yield a characteristic foul odour, which is not present, or is present in a much smaller degree, in mummification.

Emphysematous gangrene, which is often described as a separate variety, is only a sub-variety of moist gangrene. It depends upon the fact that the gases formed during putrefaction do not escape, but collect in the tissues, so that on pressure they yield a peculiar crackling sound and sensation ("crepitation"). Probably the micro-organism concerned in production of emphysematous gangrene is of a special kind. In the disease known as "quarter-evil" or "black-leg," which affects young cattle and sheep, an emphysematous and gangrenous condition is produced by the local action of the anaërobic bacillus of this disease (B. of quarter-evil, B. of symptomatic anthrax, B. of Rauschbrand).

The causes of gangrene are essentially connected with the circulatory system whether this is primarily or secondarily affected. Primary affections of the circulatory system leading to gangrene concern the heart or blood-vessels or both. Vascular conditions more commonly cause gangrene than cardiac conditions, since affections of the heart of sufficient severity to induce gangrene are generally incompatible with life. Nevertheless local death is at times due to heart-weakness, as, for example, in the gangrene of nose, scrotum, and penis that has been observed in severe Asiatic cholera. Amongst causes of gangrene acting indirectly by way of the blood-vessels, we must reckon irritants of all kinds. For irritants not only induce degenerative changes in the tissue-cells upon which they act, and thereby lower their powers of resistance, but also they lead to inflammation, with the stasis and output of exudation that this condition implies. In some cases the irritant is sufficiently severe to kill the tissues apart from inflammation; this is seen in the gangrene that follows exposure to severe cold (frost-bite), but even here it is more common for inflammation to aid in the process. Where any general condition obtains which leads to impaired vitality of the tissues (*e.g.*, glycæmia), gangrene supervenes as the result of relatively slight causes; this is well seen in "diabetic" gangrene, noma, etc.

(ii.) **Coagulation-necrosis.**—The description of this variety of local death we owe to Weigert. He showed that in most cases when a tissue, rich in protoplasm, dies, if death has occurred with sufficient rapidity to forestall the appearance of degenerative (*e.g.*, fatty) changes, the tissue becomes coagulated and the cellular protoplasm somewhat resembles strands of fibrin. For the occurrence of this change a coagulable fluid in the tissue is necessary, and this is amply present in the form of lymph. Moreover coagulation-necrosis generally occurs in inflamed tissues, or at least inflammatory processes are going on in the neighbourhood of the dead mass, and under these conditions the lymph and blood are abnormally coagulable. The onset of coagulation is brought about by the action of some substance, liberated from the cells at their death, upon the coagulable fluid. Halliburton has shown that a nucleo-albuminous substance can be prepared from many tissues which rapidly brings about coagulation of blood or lymph.

Coagulation-necrosis is the most common form of local death; it occurs, for example, in the formation of infarcts, of diphtheritic "false membranes," as an antecedent to caseous degeneration of tumours and glands. The changes that occur in or around a part that has undergone coagulation-necrosis depend upon its size, but even more upon its septic or aseptic condition. To changes of this nature sufficient reference has already been made.

(iii.) **Colliquative-necrosis.**—In this variety of local death the necrosed tissue liquefies. Probably in some cases liquefaction is preceded by coagulation as in the case of croupous pneumonia or in the central liquefaction of aseptic thrombi, and the liquefying agent is either a bacterial or a non-bacterial ferment. But in the brain, necrosis is colliquative from the first. The reason of this peculiarity is sought, by Cohnheim, in the absence of coagulable material in the brain substance itself. By Mott, it is ascribed to the fact that "the cerebro-spinal fluid which probably represents the lymph of the central nervous system is a non-coagulable fluid."

(iv.) **Fat-necrosis.**—Fat-necrosis is a condition in which localised death occurs of the fatty connective tissue in the abdominal cavity. Foci of necrosis are found in the sub-peritoneal fat, most commonly in the neighbourhood of the pancreas. The condition was first adequately described by Balser, who considered that it is due to a proliferation of fatty tissue which, as in the case of cell proliferation in tubercular nodules, undergoes necrosis from deficient nutrition. Chiari pointed out the presence in the degenerated fat-cells of hard, glistening bodies, having the appearance of lime. Balser thought that these substances are impure fat, but Langerhans denies this, because they fail to yield the characteristic osmic acid reaction of fat; he holds that they are lime salts of fatty acids. Against this view is the fact that lime salts of fatty acids are very rarely found except in the intestine, but, according to Virchow, they may occur in the metamorphosis of fatty tumours. Langerhans considers that fat-necrosis begins with destruction of neutral fat, that the fluid constituents are eliminated, but the fatty acids remain and combine with lime. Whole lobules may thus form a dead mass which is dissected out by a surrounding inflammation, but commonly the foci of necrosis are smaller.

The cause of fat-necrosis is very obscure. In a large number of cases the condition has been found along with severe changes in the pancreas, *e.g.*, gangrenous pancreatitis (von Bonsdorf, Sievers, Middleton), abscess (Rolleston), hæmorrhage (Rolleston), but this is not always the case. Hildebrand and Dettmar examined the question experimentally. They found that interference with the pancreas, whether it consisted in obstruction of the duct, in obstruction of the duct and blood-vessels, or in outlet of pancreatic secretion into the peritoneal cavity, led to typical fat-necrosis in the pancreas, appendices epiploicæ, and mesentery. They consider that the condition is due to the action of the lipolytic ferment of the pancreas (steapsin) which directly or by diffusion reaches the parts affected. Flexner, also investigating the question experimentally, finds that in early stages steapsin, which is absent from the normal fat, is present in foci of fat-necrosis. Rolleston thinks that the change is trophic and depends upon a disturbance of sympathetic innervation. Mott is of opinion that the process is due to infective micro-organisms.

**III. The Degenerations and Infiltrations.**—The *theoretical* difference between a degeneration and an infiltration is easily stated, for the former is a tissue metamorphosis, the latter is a deposition of some substance in an otherwise unaltered cell. But *practically* it is often impossible to distinguish between the two processes, partly because they may proceed side by side, partly because in many cases the histological appearances are compatible with either explanation. This is well seen in the change which is accompanied by the presence of fat-globules in liver-cells. We know that fat can be formed from proteid; we know, too, that when much fat or carbohydrate is given in the food, fat is deposited in the liver-cells. Hence, though, in a given case, we can easily see microscopically that the liver-cells contain fat-globules, it may be quite impossible to tell whether they have been formed *in situ* from degeneration of hepatic protoplasm, or are of extraneous origin and have simply been deposited there. For this reason we shall speak generally of "changes," reserving the terms "degeneration" and "infiltration" for cases in which they may be used with something approaching to accuracy. We shall discuss (i.) fatty changes, (ii.) the lardaceous change, (iii.) colloid, mucoid, and hyaline changes, (iv.) cloudy swelling, (v.) calcification, (vi.) pigmentary changes.

(i.) **Fatty Changes.**—In certain situations fatty changes are physiological. Thus in the normal storage of fat in adipose tissue we probably have an infiltration process. The breaking down of protoplasm into the colostrum of milk, the formation of fat in the uterine muscle after parturition, are true cases of fatty degeneration. In both of these examples the cause is the same, viz., a deficient blood-supply. The central mammary cells degenerate because the rapidly growing basal cells of the acini appropriate the nutriment; the uterine muscular fibres degenerate because changes in the intima and media of the uterine arteries have obstructed or obliterated their lumen. These examples serve for all kinds of fatty degeneration. The constituent of blood, which is of fundamental importance in connection with fatty degeneration, is oxygen. Wherever, in pathology, we meet with fatty degeneration, we find evidence that oxygenation has been deficient.[1]

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[1] The formation of fat from proteid has been regarded as a process of hydration and as a process of oxidation. Gautier, who holds the former view, suggests that the change is expressed by the formula:

$$\underset{\text{(Albumin.)}}{C_{72}H_{112}N_{18}O_{22}S} + 14H_2O = \underset{\text{(Urea.)}}{9N_2H_4CO} + \underset{\text{(Tripalmitin.)}}{C_{51}H_{98}O_6} + \underset{\substack{\text{(Lactic acid}\\\text{or Carbohydrate.)}}}{C_3H_6O_3} + 9CO_2 + S;$$

Chauveau, who holds the oxidation view, suggests the following series of changes:

$$4C_{72}H_{112}N_{18}O_{22}S + 139O_2 = \underset{\text{(Stearin.)}}{2C_{57}H_{110}O_6} + 36N_2H_4CO + 138CO_2 + 42H_2O + 4S,$$

the stearin is again oxidised,

$$2C_{57}H_{110}O_6 + 67O_2 = \underset{\text{(Glucose.)}}{16C_6H_{12}O_6} + 18CO_2 + 14H_2O,$$

Pathological fatty degeneration is met with either as the result of local or of general causes. As examples of local fatty degeneration may be instanced the caseation that occurs in nodules of tubercle, in gummata, in patches of atheroma, or in the centre of new-growths. The cause is in all cases the same, a proliferation of cells without a corresponding increase of blood-vessels to supply them with nutriment, or with obliteration of those blood-vessels that are already formed. Nevertheless, there is reason to believe that the cell itself plays a part in the process, for the fatty changes that occur in cartilage and nerve-cells in old age, and in leucocytes when they become "pus-cells," seem to imply that with lowered vitality the cell is no longer able to resist the breaking down of its protoplasm into fat. Localised fatty changes also occur in muscles that are cut off from their nervous supply. In these cases the fat is present not only in the inter-muscular connective tissue but also in the muscular fibres themselves. The change in the muscular fibres is certainly degenerative, but whether the fat in the inter-muscular connective tissue has been formed by degeneration of connective tissue cells or has been deposited there from muscle, it is impossible to say; the latter, however, seems more probable.

The chief general conditions leading to fatty changes are (*a*) anæmia, (*b*) poisons of certain kinds, (*c*) high temperature. Though these causes are general, the fatty change is often localised in few regions, the liver, kidneys, and heart being the most important. In these cases the fatty change is commonly a degeneration.

and the glucose is oxidised to $CO_2 + H_2O$. In the absence of sufficient oxygen to carry out the whole change, decomposition of proteid would therefore form reserve fat. With regard to the formation of fat from carbohydrate, Gautier suggests

$$\underset{\text{(Glucose.)}}{14C_6H_{12}O_6} = \underset{\text{(Stearin.)}}{C_{57}H_{110}O_6} + 24CO_2 + 27H_2O + C_3H_4O_3 .$$

Hanriot suggests

$$13C_6H_{12}O_6 = \underset{\substack{\text{(Oleostearo-}\\ \text{palmitin.)}}}{C_{55}H_{104}O_6} + 23CO_2 + 26H_2O .$$

On the subject of the origin of fat in animals, a paper by Kauffmann (*Arch. de Physiol.*, vol. viii., 1896, p. 757) may be consulted.

(*a*) *Anæmia.*—The anæmias show marked differences with regard to the occurrence of fatty changes. Pernicious anæmia is perhaps the most important cause of fatty degeneration of heart muscle, but in chlorosis, though the anæmia, as measured by the amount of hæmoglobin and the number of red blood-corpuscles present in the blood, may be as severe as it is in pernicious anæmia, the heart muscle is generally unaltered. In chlorosis the tendency to fatty change is expressed by a marked deposition of fat in the subcutaneous tissues.

In pernicious anæmia and other grave forms of anæmia, though the heart muscle may be so greatly affected that the change becomes macroscopic ("tabby-cat" striation), other muscle in the body is unaffected. The reason for this, as Mott suggests, probably lies in the fact that the functional activity of heart muscle cannot, like that of voluntary muscle, be lowered in accordance with the diminished supply of nutriment, but is rather increased owing to a number of subordinate conditions. Hence the heart muscle is called upon to do more work than normal upon a diminished supply of nutriment, with the result that its vital resistance is lowered and it undergoes change. Mott supports this view by his observation that in pernicious anæmia the diaphragm also shows fatty degeneration. Since this muscle, like the heart, is called upon to an abnormal extent in this disease owing to the readiness with which dyspnœa is called forth by slight exertion, the confirmation that it yields is strong.

(*b*) *Poisons.*—Of the poisons leading to fatty degeneration, bacterial toxins are clinically among the most important, because they are among the most common. Thus Sidney Martin, and Mott have shown that diphtheria toxin produces fatty degeneration of muscle, and Scagliosi has shown that, in the heart, the poisonous action commences with alteration of the vessel wall, which is followed by nervous and muscular changes. Further, Baldassari found in rabbits that the toxin attacks the nuclei of liver- and kidney-cells, and this observation is confirmed by Barbucci. Hence in the case of diphtheria there is ample evidence that vascular, cellular, and nervous processes are at work, all of which tend to produce degenerative changes. It is probable, too, that the fatty changes occurring in pus-cells and in tubercular nodules are, in part, due to the action of toxins, and the same explanation may ultimately be found to hold for the intense fatty degeneration of the liver that occurs in "acute yellow atrophy" of that organ.

Fatty degeneration also occurs as the result of poisoning by phosphorus, by arsenic, by carbonic oxide and some other substances. In these cases the fatty change is seen in liver, heart, kidneys, and voluntary muscles, and is usually very intense.

In this category alcohol must also be mentioned. Alcoholism may lead either to fatty changes in the liver or to great deposition of fat in the subcutaneous tissues. In the former case it is probable (as we shall see when considering cirrhosis of the liver) that the alcohol acts as a protoplasmic poison. In the latter case it is doubtful whether the fatty change depends upon alcohol at all, for obesity is commonest in beer-drinkers, who take, in their liquor, comparatively little alcohol but much sugar. Spirit-drinkers, who take comparatively much alcohol and little sugar, suffer from cirrhosis of the liver with its accompanying fatty changes, but they are generally emaciated. The subcutaneous fat of the beer-drinker must probably be looked upon as reserve material (though undoubtedly of an inferior kind), the hepatic fat of the spirit-drinker as degenerated protoplasm.

(*c*) *High Temperature.*—It has long been known that exposure for some time to external warmth is followed by fatty changes. When conjoined with a plentiful supply of food and with restricted movement, it was employed as a means of fattening animals for the table long before the question of its scientific meaning was broached. We know that in patients dying of febrile disease, fatty changes are common in the liver and kidneys. In hyperthermia, too, it is generally agreed that the same is the case (Liebermeister, Litten, Werhowsky, Ziegler, etc.), but Naunyn, relying on his own experiments, opposes this view. Werhowsky and Ziegler placed rabbits in a thermostat at a temperature of 36°–40° C. for periods varying from two to twenty-nine days, and found that, besides other changes, there occurred fatty degeneration of liver and later of kidneys and heart. Ziegler, however, hesitates to apply the results obtained on hyperthermic rabbits directly to pyrexial man, and in particular he does not feel justified in ascribing fatty changes in fever merely to rise of temperature, for other agencies are probably also at work. On the whole, however, evidence seems to indicate that rise of temperature alone is able to produce fatty change, but under these circumstances the change bears more resemblance to a physiological storage of fat than to a pathological degeneration of protoplasm.

Before leaving the fatty changes we must briefly consider the ways in which some of the above-mentioned causes act. In the more strictly pathological conditions, *i.e.*, in fatty degeneration, we certainly have to deal with a change involving proteid metabolism, but in those conditions which approximate more to a physiological storage of fat, *i.e.*, fatty infiltration, obesity, etc., we are ignorant whether we have to deal with a direct conversion of carbohydrate into fat, or a storage of fat derived from the food, or whether the fat is really of proteid origin, the expenditure of which has been covered by combustion of carbohydrate or of previously stored fat. Leaving the question of fatty infiltration on one side—as no answer to it can at present be given—we will confine our attention to fatty degeneration.

We have evidence, at least in the case of poisoning by phosphorus and by carbonic oxide, that there is increased destruction of proteid. For Voit and Bauer showed that, when a starving dog is poisoned with either of these substances, the production of fat is accompanied by an increased output of urea. Oxidative processes are diminished, for they found that the intake of oxygen and the output of carbonic acid are below normal. Since the animal in these cases is starving, it is clear that the fat present has not been derived from food, nor is it pre-existing fat or fat formed from previously stored glycogen, for in starvation all reserve fat and glycogen are rapidly used up. Moreover the increased output of urea is positive evidence as to the origin of the fat from proteid.

We will deal with the two poisons separately. Since carbonic oxide forms a more stable combination with hæmoglobin than does oxygen, poisoning with carbonic oxide produces a condition essentially the same as anæmia so far as oxygenation of the tissues is concerned. But deficient oxygenation, if prolonged, leads to lowered vitality of cell-protoplasm, and therefore it is probable that in carbonic oxide poisoning (and in the anæmias) fatty degeneration is immediately dependent upon impaired cell nutrition. We know that in general starvation the body breaks up its own protoplasm to supply its imperative needs, and it is not unreasonable to suppose that with deficient nutrition the cell-protoplasm does the same. It would then break up into two portions, a nitrogenous and a non-nitrogenous. The nitrogenous portion will ultimately become urea, and the non-nitrogenous portion, since there is an insufficient supply of oxygen for its complete combustion to carbonic acid and water, will remain in the cell as fat.

Phosphorus poisoning also leads to deficient intake of oxygen and output of carbonic acid; oxidative processes are therefore reduced in this case also. But we are uncertain as to the exact way in which the fatty degeneration is brought about. For phosphorus does not produce an anæmia, but on the contrary a polycythæmia. It is probable, therefore, that phosphorus does not act directly through the blood. Gaule maintains that the primary change in phosphorus poisoning is in the cell nucleus, and he is supported by other authors. He believes that some of the fat may arise from formation of the phosphorus-containing fat, lecithin.[1] Mott thinks it possible that phosphorus interferes with the power possessed by cells of taking up oxygen and storing it in their protoplasm ("tissue-respiration"). Evidence has already been given that one at least of the bacterial toxins acts directly upon the cell nucleus, and it is not improbable that a considerable number of poisons, bacterial and non-bacterial, will ultimately be found to directly affect this, the centre of cell life and change.

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[1] Cohnheim denied that lecithin can be broken up so as to yield a neutral fat, but Mott, from recent investigations (*loc. cit.*, p. 189), concludes that such a change can take place and is important in fatty changes occurring in nerve matter.

With regard to heat in the production of fatty degeneration, we know that heat leads to increased proteid metabolism, and we also know that external warmth diminishes the necessity of metabolism for the maintenance of body temperature. When, therefore, an animal is exposed to external heat, we have a condition in which much proteid is broken down, but little is oxidised. These are conditions under which we should expect fat to be produced. Further, we should expect it to be more marked if the supply of oxygen to the heated animal is deficient. Naunyn, indeed, maintains that this is the essential factor, for he finds that rabbits may be kept in a chamber at 36°–40° C. for nearly a fortnight without showing fatty changes, provided the chamber is properly ventilated and the animal is given plenty of green food (*i.e.*, a sufficient supply of water). In fever, as distinguished from hyperthermia, toxic action on tissue cells, on nerve, and on blood, probably play a part in the production of fatty degeneration, perhaps even a more important part than the rise of temperature itself.

(ii.) **The Lardaceous Change.**[1]—The lardaceous change affects the body generally and leads to so many symptoms that it is often spoken of as "lardaceous disease." But the change itself is not a primary one, for it occurs clinically as the result of two important conditions, prolonged suppuration and syphilis; of these prolonged suppuration is the chief. The lardaceous change is characterised by the presence of a substance known as "lardacein" in the walls of small blood-vessels, especially the arterioles and capillaries, and perhaps also in some other situations.

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[1] The lardaceous change was first described by Virchow in 1851, under the name of "amyloid degeneration" from the fact that the lardaceous material, when subjected to the action of iodine followed by sulphuric acid, yields a colour change which recalled to him the blue colour produced by the action of iodine on starch. But the lardaceous material is not starch nor even allied to starch, while the colour reaction with iodine and sulphuric acid is a bluish-black, and is produced by the interaction of iodine and sulphuric acid quite apart from lardacein. The name "amyloid" is therefore misleading, and though it is still commonly employed, and especially in Germany, it has never gained much foothold in this country. The change has also been called "waxy," "albuminous," "albuminoid," but the name "lardaceous" has received official recognition in England by the Royal College of Physicians.

(*a*) *Lardacein.*—Lardacein is a colourless, semi-translucent, homogeneous substance, containing nitrogen. So far as its percentage composition is concerned, it is closely allied with proteid generally. It differs, however, from proteid in that it contains somewhat less nitrogen, a great deal less potassium, but a slightly greater percentage of alkaline earths. In its properties it differs markedly from proteid generally: it is insoluble in water, in saline solution, in dilute acids and alkalies, though on treatment with strong acids or alkalies it is converted into acid- or alkali-albumin. It does not undergo peptic digestion, or at least not readily, for Kostjuria and E. Ludwig have shown that it goes into solution if presented to the enzyme in a very fine state of division.

Lardacein in tissues has two highly important and characteristic staining reactions which differentiate it from proteid generally. With iodine in solution, it stains mahogany-brown, whereas unaffected tissues stain canary-yellow; with methyl violet it stains rose-pink, the tissues generally staining a bluish-violet. The reaction with methyl violet is a relatively constant one, but the iodine reaction is lost at once if the tissue affected with the lardaceous change is treated with alcohol or with solutions of the caustic alkalies, even though dilute. The macroscopic and microscopic appearances of the material remain unaltered, but no method is known whereby the lost iodine reaction can be restored. Though the general appearance of lardacein is very constant, hardly any two specimens of lardaceous tissue yield exactly the same staining reactions. Since we must regard staining reactions in most cases as representing chemical combinations, we must probably conclude that lardacein is not a single substance of uniform chemical composition. As to its relationship with the hyaline material found in the hyaline change (which macroscopically it greatly resembles) we are ignorant, but so far as staining reactions are concerned one can, by selecting specimens, demonstrate a series of intermediate conditions between typical hyaline material on the one hand, and typical lardaceous material on the other. But whether one can argue from this fact, and others of a like nature, that hyaline material is at one end of a series of changes at the other end of which stands lardacein, it is at present impossible to say.

(*b*) *Seats of Lardaceous Change.*—It has already been said that the lardaceous change is a general one, but certain organs and tissues are more commonly affected than others. The following table drawn up by Dickinson illustrates this point:—

*Frequency with which Various Organs and Structures were found to be Lardaceous in* 118 *Cases of Lardaceous Disease examined post-mortem* (*Dickinson*).

| | |
|---|---|
| Kidney, | 95 |
| Spleen, | 76 |
| Liver, | 65 |
| Intestines, | 35 |
| Stomach, | 9 |
| Supra-renals, | 9 |
| Lymphatic glands, | 5 |
| Pancreas, | 1 |
| Thyroid, | 1 |
| Œsophagus, | 1 |
| Testes, | 1 |
| Endocardium, | 1 |

In these organs and tissues the change is seen first and to the greatest extent in the blood-vessels. In the kidney it affects principally the glomerular tufts; in the liver the intermediate zone of the lobule, *i.e.*, that supplied by the hepatic artery; in the spleen, either the Malpighian corpuscles ("sago-spleen"), or in some cases the vessels in the fibrous trabeculæ of the organ. It is much less commonly seen in veins than in arterioles and capillaries. In the arterioles it is the middle coat that suffers, though whether the change commences in connection with the unstriped muscle or in connection with the fibrous tissue of that coat, it is impossible to say.

From the fact that kidneys, intestines, stomach are affected, lardaceous disease presents us with symptoms of albuminuria and dropsy, diarrhœa, and vomiting. We shall not delay over these conditions, for they are due to excessive transudation (though perhaps also in some degree to diminished absorption), and upon this subject sufficient has already been said. Though the hepatic and splenic changes are among the most common, and are certainly among the most intense, we cannot point to any symptom that they produce, unless it be ascites in a few instances. In the kidney and liver the lardaceous change is often associated with fatty changes. In the kidney an acute or subacute nephritis is frequently superadded.

(*c*) *Experimental Investigations.*—Positive or strong presumptive evidence of suppuration was present in 83 per cent. of the cases in which lardaceous changes were found on post-mortem examination at St George's Hospital between the years 1867 and 1894 (Dickinson). The causal relationship between prolonged suppuration and lardaceous change in man is allowed, and animal experiments have been made on the point, though it must be confessed that the majority of them are far from conclusive.

Birch-Hirschfeld maintained that he produced the lardaceous change in a rabbit by injecting the pus from a boy suffering from caries of the tibia; Charrin maintained the same after causing suppuration in rabbits with *B. pyocyaneus.* But the most important work on the subject is that of Krawkow. Krawkow injected into rabbits (amongst other animals) virulent cultures of *Staph. pyog. aureus*, and states that in most cases, after a suppuration extending over one to two months, the spleen, salivary glands, intestines, liver, and kidneys,[1] were lardaceous; in frogs, under similar treatment, he obtained traces of the change in the spleen. Filtered cultures of the micro-organisms were ineffective, as was suppuration caused by chemical irritants, such as turpentine. He therefore associates the change with actual presence of living micro-organisms themselves.

Krawkow's work, however, presents difficulties. Thus he found that the "lardaceous" organs were soft and friable; in man, at all events, they are exactly the reverse, so much so that lardaceous liver was at one time recommended as an embedding material for histological purposes. Moreover, his "lardaceous" substance is soluble in water and in alcohol. Lastly, Taylor, working in the Cambridge Pathological Laboratory, has never been able to find, either macroscopically or microscopically, the least trace of any substance that, by its appearance or its staining reactions, could be regarded as lardaceous. And that, too, even in rabbits that had suppurated continuously and fairly profusely for nine months.

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[1] The tissues are given in the order of frequency with which the change was observed.

Recently, however, Davidsohn has published experiments confirming Krawkow. Using rabbits, mice, fowls, guinea-pigs, and cats, and injecting into them subcutaneously, every two or three days, cultures of staphylococci, he found that the lardaceous change manifested itself in about half the cases. He obtained the best results with rabbits and mice; in the case of guinea-pigs and cats he obtained no lardaceous change whatever.

With regard to the length of time that must elapse between the onset of suppuration and death with lardaceous disease in man, Cohnheim found that the shortest time is two to three months. Dickinson (*loc. cit.*, p. 271) speaks of a case in which a previously healthy man died three weeks after undergoing amputation for a compound fracture. During the period he suffered from profuse suppuration and pyæmia, and after death early lardaceous change was found in the kidneys. With reference to the connection between syphilis and lardaceous disease, little can be said, but there is no doubt that, rarely, syphilis may be followed by lardaceous disease quite apart from considerable suppuration. From Dickinson's tables this would appear to obtain in about 12 per cent. of lardaceous cases. But syphilis, accompanied and not accompanied by considerable suppuration, accounted for about 20 per cent. of his cases. Tuberculosis, whether of lung or of bone or of other regions, accounted for nearly 50 per cent.

(*d*) *Nature of the Lardaceous Change.*—It is uncertain whether the lardaceous change is a degeneration or an infiltration, or a combination of the two. There are four chief views as to its ætiology, (1) that it is a direct degeneration, (2) that it is a retrogressive metamorphosis of tissue, (3) that it is an infiltration with lardacein or a precursor of lardacein, (4) that it is a degeneration of tissue *and* an infiltration from the blood. Virchow considers that the blood has undergone a chemical change in its soluble constituents, as a result of which the tissues undergo retrogressive metamorphosis, and are filled up with an iodine reacting substance which is laid down in them in the same way as lime salts are laid down in calcification. Cohnheim regarded it as a local degeneration of the pre-existing albumin of the tissue, Rindfleisch as a substance deposited from the blood. Ziegler considers it as a deposit between cells, but allows that epithelial cells may, rarely, become lardaceous. Wichmann holds that "it occurs in organs whose tissues are already injured in their physiological relations by disease, and have become unable, by reason of the anæmia, etc., to assimilate normally the albumin brought by the blood; this albumin infiltrated into the tissue spaces, remains there, and sooner or later undergoes chemical change, partly by combination with other proteid bodies or their derivatives." Czerny believes that the lardaceous material, or a precursor, is conveyed to the tissues by leucocytes, which are themselves pathological. Krawkow regards the change as a degeneration produced by the action of microbial products on those organs which are most important in the struggle of the organism against microbes and their toxins (spleen, liver, lymphatic glands), and on those organs that excrete the poison (kidneys and intestines). The very diversity of views indicates that at present we have not sufficient data for arriving at a thoroughly satisfactory conclusion on the question; for this reason we have spoken of the "lardaceous *change*" throughout.

(iii.) **Colloid, Mucoid, and Hyaline Changes.**—We shall not devote much space to the consideration of these changes, for at present they are but little understood and therefore lack definiteness. It is very difficult to appreciate the particular changes indicated by each writer on the subject, for the "colloid" of one author is often included under the "hyaline" of another, and so on.

All the changes are changes of albumin, for colloid, mucoid, and hyalin are nitrogenous substances allied with albumin. Speaking generally, the substances are semi-translucent and more or less homogeneous in structure.

(*a*) **Colloid** is derived from epithelium. In its properties it is very like mucus, but differs from mucus in that it has commonly a yellow or brown colour, does not swell up in water, is not coagulated by acetic acid, and is not rendered cloudy by alcohol or by chromic acid. Physiologically, it is found in the thyroid body; pathologically, it occurs in cystic goître, in many forms of carcinoma, especially those originating from stomach and intestines, and in cysts that have been formed by occlusion of ducts lined by epithelium, *e.g.*, in the kidney. According to Mallory, the change has a tendency to affect the cerebral blood-vessels, whether it occurs in the middle coat of larger vessels or in capillaries that form net-works in certain portions of the brain. Under all circumstances, however, Mallory finds that colloid material in the brain has a great tendency to undergo calcification, whereby it leads to atrophy of nervous tissue and formation of sand-like deposits or stone-like concretions.

(*b*) **Mucus** is derived from epithelium and from connective tissue; from epithelium by a transformation of mucigen granules (as in the case of mucous glands), or by a transformation of cell-protoplasm (as in the case of goblet-cells), from connective tissue by a metamorphosis and swelling of the ground substance. It is thus a wide-spread change. Physiologically, formation of mucus from cells is so common that examples need not be given, formation from connective tissue is best seen in the case of the umbilical cord. Pathologically, an excessive formation of mucus is seen in catarrhal inflammations of mucous membranes; here the mucus is of epithelial origin. When affecting the connective tissue, the mucoid change is seen under the most varied conditions, for the change may be undergone by fibrous tissue, cartilage, bone, sarcoma cells, in fact by any material belonging to the connective tissue group. Mucus is not a substance of uniform composition; nor even is its underlying constituent "mucin" a single substance, for the composition of mucin varies according to the origin of the mucus from which it is derived. The mucins, however, agree in that they all swell greatly in water, are precipitated by alcohol and by acetic acid, are soluble in neutral salt solutions, and in solutions of the alkaline hydrates and carbonates. They also yield on suitable treatment a copper-reducing substance of carbohydrate nature, which is, in all probability, a true sugar. According to Pfannenstiel the contents of proliferating glandular ovarian cysts and in part also of papillary ovarian cysts is a "pseudo-mucin" formed from the cells lining the cyst. Probably there are also several "pseudo-mucins," but into questions of this kind it is impossible to enter here.

(*c*) The **hyaline** change was originally described by von Recklinghausen as a sub-division of "colloid degeneration." He found the change widely spread in the body, but under the name he included conditions that would now be placed under different headings, *e.g.*, colloid, coagulation-necrosis, etc. Ernst has endeavoured to give precision to the terms "hyaline," "colloid," and "mucoid" by laying stress on their staining reactions. In this direction much may be hoped for. Ernst finds if a section of thyroid gland, for example, be stained by a special method involving the use of picric acid, acid-fuchsin, and hæmatoxylin, that three substances can be distinguished: colloid, which stains orange-red and is invariably intra-follicular; hyaline, staining purplish-red and extra-follicular; mucin, which stains flesh-pink. He therefore gives a definiteness to the term "hyaline," but it does not necessarily correspond with a hyaline *appearance*; thus the hyaline renal casts, commonly so-called, are not hyaline in Ernst's sense of the term: he calls them "homogeneous." Von Recklinghausen considered that the hyaline change is a cell-degeneration. Ziegler describes a hyaline change of connective tissue which in appearance and in seat of election is very similar to the lardaceous change, but which differs from it in not yielding the characteristic staining reactions.

It is clear from the foregoing paragraphs that much work must be done before any very definite statement can be made with regard to colloid, mucoid, and hyaline changes. Apparently, however, they are more akin to the degenerations than to the infiltrations.

Mention may be made in passing of a change seen in certain muscles (*e.g.*, rectus abdominis) under various pathological conditions, but especially along with continued fever. It is known by the name of Zenker, who first described the condition, but other names are "waxy" and "vitreous." The term "waxy" is objectionable, because it is also applied to the lardaceous change. In Zenker's degeneration the muscular fibres themselves look dull and semi-opaque, and microscopically are found to have lost their striation, so that the sarcolemma is filled with masses of clear, homogeneous substance; the connective tissue cells of the muscle undergo proliferation. By some authors the change is regarded as a coagulation-necrosis.

(iv.) **Cloudy Swelling** (granular, albuminous or parenchymatous degeneration).—Cloudy swelling is a cellular change the principal seats of which are the liver, the kidneys, and the heart. It occurs in patients who before death have been the subjects of infective disease with high fever. The change, however, is not produced by the rise of temperature, but by the action of toxins. Since cloudy swelling is the earliest sign of poisoning by phosphorus, arsenic, carbonic oxide, etc., it is not only bacterial poisons that are effective.

The change is well characterised by its name, for the affected cells are larger than normal, their contour is indistinct, and their protoplasm cloudy from the presence of innumerable minute granules of albuminous nature; often the nucleus is completely obscured. The granules are soluble in acetic acid and in caustic potash, but insoluble in ether, and as, in addition, they do not stain black with osmic acid, they are not fatty. There is no doubt, however, that they are on the way to become fat, for cloudy swelling and fatty changes may be met with side by side, and conditions which, if acute, produce cloudy swelling, if protracted, produce fatty degeneration. According to Cohnheim, Ziegler, and others, cells may recover from cloudy swelling, if not too advanced, but this is only a probability for which we have no definite evidence. Macroscopically the affected organ is enlarged and lustreless and often anæmic; it looks as if it had been cooked. When the change affects the heart, as it does in myocarditis, cardiac function is seriously impaired.

(v.) **Calcification.**—Calcification is a process of infiltration; the calcium salts are carried in solution to the tissues by the blood and lymph, and deposited therefrom in the solid form. The salts concerned in calcification are chiefly the phosphate and the carbonate of lime, with small amounts of the corresponding magnesium salts and some others. They are therefore identical with the salts present in bone. The salts are deposited either in cells or in inter-cellular substance. The deposition more commonly affects inter-cellular substance, but calcification of cells occurs and sometimes can be well seen, as, for example, when it affects ganglion cells of the brain in old age.

Apart from the deposition of calcium salts in masses of degenerated or dead tissue—to which reference will be made immediately—calcification is a sign of senescence. But the number of years that have passed over the patient is not the only factor to be considered; it is more strictly just to say that calcification signifies old age of the particular tissue in which it occurs, for calcareous plates may be found in the aorta of an otherwise healthy man of thirty years.

In many instances the change is rather physiological than pathological. The calcification, for example, that occurs in the costal and laryngeal cartilages of the aged is a physiological preliminary to ossification of those cartilages. But in other cases the change is distinctly pathological. Such, for example, is the calcification of the walls of arteries constituting arteritis deformans, the calcification that sometimes occurs and may even go on to true bone-formation in inter-muscular septa, the calcification of tendons, calcification of the placenta, etc.

Calcification is a secondary and not a primary process, for putting aside calcification associated with normal bone-formation, calcium salts are never deposited in perfectly healthy tissues, but only in tissues the vitality of which has been lowered or extinguished.

Dead and degenerated tissues, when situated among living tissues, frequently become calcified. This is typically seen in the formation of lithopædion, a rare condition in which a fœtus that has escaped from an ectopic gestation is retained in the abdominal cavity for years and is infiltrated with lime salts. It is also seen in the calcification that often succeeds death and caseation of the cells in a tubercular nodule or a patch of atheroma, or death of the central portion of a tumour (*e.g.*, fibromyoma). Of the same nature, practically, is the calcification of dense inflammatory fibrous tissue to which we have already referred (p. 297), when discussing the means whereby the organism renders an irritant innocuous. When the calcium salts are deposited in a mass of caseous or otherwise disintegrated tissue, there can be no question of intra- or extracellular deposition, and the mass is simply more or less gritty.[1]

The reason for deposition of calcium salts is not clear. In particular, the fact that tissues (*e.g.*, tubercular nodules, central portion of hard fibro-myomata) which are ill supplied with blood or lymph are nevertheless the especial seats of calcification is difficult to reconcile with the fact that the calcium salts are carried to the part by blood or lymph. We can understand, too, that blood-vessels should often be the seats of calcareous change, but why should calcification affect arteries with extreme readiness but veins with such rarity that calcification affecting the walls of veins is a pathological curiosity? If we seek the explanation in the relative amounts of carbonic acid held by arterial and by venous blood, and consider that the large quantity of carbonic acid in venous blood keeps the calcium salts in solution, and that the small quantity in arterial blood favours their deposition, we are met by the fact that the pulmonary veins carry blood having the lowest percentage of carbonic acid in the body and yet calcification is almost unknown in these vessels. Moreover, the assumption that carbonic acid increases the solubility of calcium salts is only founded on the fact that water containing that gas holds in solution an increased amount of calcium carbonate. But in the first place blood and lymph are not water, and in the second place calcium carbonate is not the most important constituent of calcareous deposits. Probably the explanation in this particular case lies in the fact that calcification in blood-vessels is closely bound up with antecedent atheroma or arterio-sclerosis, and these changes almost exclusively affect arteries. But this only shifts the difficulty back to the question why atheroma and arterio-sclerosis are diseases of arteries and not of veins. We are probably correct in ascribing great importance to high blood-pressure and the stress to which it exposes the vessel wall, in the causation of these two morbid conditions, but further than that we cannot go.[1]

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[1] Calcium salts show a marked affinity for hæmatoxylin, with the result that, when microscopic sections of tissues in which they are present are stained with this reagent, they show a granular and densely stained deposit of hæmatoxylin at those points where the calcium salts are situated. This may easily be mistaken for careless staining or insufficient washing in distilled water, unless the fact be recognised.

(vi.) **Pigmentary Changes.** — Abnormal pigmentations depend upon the presence of (1) pigments intrinsic to the body, or (2) extrinsic pigments. The intrinsic pigments are (*a*) hæmatogenous, (*b*) non-hæmatogenous.

(1) *Intrinsic Pigments.* (*a*) *Hæmatogenous.*—When red blood-corpuscles are broken up in quantity two substances may be formed, hæmosiderin, which contains iron, and hæmatoidin, which is iron-free. These substances may remain *in situ* or may be carried to distant parts.

Hæmosiderin is a substance in which the iron presents the characteristic chemical reactions of iron; it turns black in the presence of ammonium sulphide from the formation of sulphide of iron, forms Prussian blue in the presence of potassium ferro-cyanide and hydrochloric acid. It therefore differs from iron-containing substances such as hæmoglobin, ferratin, etc., in which the iron is "masked." By aid of the reagents just mentioned, large quantities of iron may be recognised in the liver in pernicious anæmia; it lies in the hepatic cells in the form of minute granules and is seen especially in the intermediate zone of the lobule, *i.e.*, that supplied by branches of the hepatic artery. In pernicious anæmia (as also in malaria, or indeed under any condition in which there is marked hæmolysis, *e.g.*, poisoning by arseniuretted hydrogen, toluylenediamin) hæmosiderin may also be found in larger or smaller quantities in the spleen, in renal epithelium, in medulla of bone, and elsewhere. The black colour seen in tissues that contain much blood when they are undergoing putrefaction, depends upon the action of sulphuretted hydrogen upon hæmosiderin.

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[1] In reference to the important bearing of coagulation upon calcification, it may be mentioned that Litten found that if the blood be allowed to flow through a kidney, the artery of which has been ligatured for an hour and a half, there is a precipitation of calcium salts "to such an extent that the organ may become as hard as stone." The observation is quoted by Mott, but such a condition is certainly not constant. In three dogs in which I performed the experiment no deposition of calcium salts was observed, even on microscopic examination. My experiments are hitherto unpublished and were performed with a different object.

Hæmatoidin is occasionally found in a crystalline or a granular form in old extravasations of blood, *e.g.*, in cerebral apoplexy. Sometimes it is free, sometimes contained within leucocytes or other cells. When crystalline it forms minute rhombic plates of an orange colour. There is doubt, both in the case of hæmosiderin and in that of hæmatoidin, how far the agency of living cells enters into formation of the pigment, but probably Neumann is correct in his belief that living cells are necessary to the formation of hæmosiderin, but unnecessary to the formation of hæmatoidin.

The pigmentation around syphilitic and other ulcerations, that seen over the tibiæ of persons who sit much in front of the fire (ephelis ab igne) are hæmatogenous. Where the part is poorly supplied with blood-vessels and lymphatics, pigmentation often persists for long periods. Derivatives of blood-pigment are of different colours; to this fact is due the series of colour-changes undergone by a bruise. The yellowish skin-coloration seen in the subjects of pernicious anæmia has been ascribed (but incorrectly) to presence of the urobilin which is formed in large quantities in this disease. Highly important in connection with hæmatogenous pigmentations are the derived pigments bilirubin and biliverdin. The yellow or green coloration of tissues in jaundice is due to their impregnation with these substances. Occasionally bile-pigments are deposited in a crystalline form. To these points further reference is made in connection with the subject of jaundice.

(*b*) *Non-hæmatogenous Intrinsic Pigments.*—The most important of these pigments is melanin. It is iron-free and can only be formed by the agency of living cells. It is found in the cells of melanotic sarcomata, which probably always originate in tissues where pigment-formation is normal (*e.g.*, choroid coat of eye). Melanin granules vary in colour from a faint yellow to an intense black. When melanotic sarcoma affects the urinary tract melanin may be passed with the urine.

Abnormal formation of a normal pigment may also account for pigmentary changes. Thus excessive formation of normal pigment probably explains the pigmentation often seen in Addison's disease, the darkening of the mammary areolæ in pregnancy, the bronzing of the skin by the sun's rays, etc. In other cases (vitiligo, anæsthetic leprosy) the abnormal coloration is probably due to a deficiency of normal pigment. In some of these examples (Addison's disease, vitiligo, leprosy) it is possible that the pigmentary changes depend upon nervous influences or their absence.[1]

(2) *Extrinsic Pigments.*—Extrinsic pigments are of most varied nature. They enter the body by lungs, alimentary tract and skin. The most common is carbon, which is inhaled in minute particles and is carried by leucocytes to all parts of the lung and thence to the bronchial glands by way of the lymphatics. Carbon leads to the condition known as anthracosis or miner's lung, from the fact that miners and others working in an atmosphere containing coal dust are especially liable to be affected. But all adults living in cities have their lungs pigmented from the same cause. In siderosis, which is due to inhalation of minute particles of iron, the lung has a rusty colour; in chalicosis, a condition affecting stone-masons, etc., the inhaled particles are white and the lung is abnormally pale. Argyria is a bluish-grey discoloration of the skin and organs that was formerly often seen owing to the favour in which silver nitrate was held for the treatment of various nervous disorders. The pigmentation is due to the deposition of metallic silver in the tissues. Lastly must be mentioned such pigments as lamp-black, vermilion, etc., used in tattooing. Much of the pigment introduced into the true skin in tattooing remains localised, but a greater or smaller amount is always found in the nearest lymphatic glands.

IV. **Atrophy and Hypertrophy.**—In general terms, it is said when a part is smaller than normal that it is atrophied, when larger, that it is hypertrophied. But certain special terms have been coined to define special conditions more closely. These are somewhat confusing, and have not been well chosen; nevertheless, they have gained acceptance, and it will be convenient at the commencement of this section to set them forth in order. In strict language, then, we have to differentiate the following conditions:—

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[1] See Chapter xiii., Sect. vii., part ii.

1. *True Atrophy*, when tissue cells, after having reached their normal size, retrograde and become smaller, the number of cells in the tissue remaining unaltered.

2. *Numerical Atrophy*, when the number of cells in the tissue which was formerly normal becomes diminished. This condition is also known as *aplasia.*

3. *Hypoplasia*, when a tissue fails to reach the normal size owing to some defect of nutrition other than a congenital one. This condition is also known as *aplasia.*

4. *Agenesia*, when a tissue is smaller than normal owing to failure of development from some congenital defect.

5. *True Hypertrophy*, when a tissue is increased in size because its component cells are individually larger than normal.

6. *Hyperplasia*, when a tissue is larger because it contains a greater number of component cells of normal size.

7. *Gigantism*, when a tissue is larger than normal because of some congenital peculiarity.

Unless it is absolutely necessary these terms will not be used in the following paragraphs, but we shall speak simply of "atrophy" and "hypertrophy." Nevertheless when they are used they will be intended to convey the significations given.

(i.) **Atrophy.**—It would simplify matters if we could fully distinguish the parts played by blood-supply, by cell, and by nervous system in the causation of atrophy, for they must all be concerned in atrophy as they are in normal nutrition. But in many cases this is impossible because we cannot decide upon the factor primarily responsible for the atrophy.

Under certain conditions atrophy is a physiological process. It is physiological in the atrophy of the pupillary membrane in embryonic life, in the atrophy of the thymus body in the second year of life, in the atrophy of the generative organs at the climacteric, in the general atrophy of old age. Even the removal of provisional callus and the absorption of redundant fibrous tissue in repair are physiological atrophies.

(1) Deficiency of blood-supply is an important cause of pathological atrophy, but the deficiency must be long continued and not too severe. For if not long continued, it may be without effect, and if too severe, it will lead to degeneration or to local necrosis. One of the most important forms of atrophy due to deficient blood-supply is "pressure atrophy." Pressure atrophy is the cause of that absorption of rib, costal cartilage, sternum that may be seen with aneurysm of the ascending part of the arch of the aorta, of the absorption of the bodies of dorsal vertebræ with aneurysm of the descending aorta, of the absorption of bone when the periosteum or medulla of bone is the seat of a malignant new-growth. The process in bone is closely allied with caries, for in both cases absorption of the bone is carried out by osteoclasts; but whereas, in caries, the osteoclasts are abnormally numerous and active, this is not the case in pressure atrophy. Here, the atrophy is due to the fact that no new bone is laid down to replace that removed by osteoclasts, owing to interference with the periosteal blood-supply by pressure of the swelling.

Many of the "disuse atrophies" probably come under this heading,—at least in part,—for disuse means lessened blood-supply. We have already referred to this point in connection with normal nutrition. Besides the examples there given, a striking example of disuse atrophy is that undergone by the lower part of the gut after lumbar colotomy; as the result of disuse, the intestine below the artificial anus may dwindle to a cord no thicker than the little finger. Deficient blood-supply, in part owing to disuse, also accounts for the diminution in size of the uterus after parturition. The wasting in this case is so marked that the normal uterus diminishes in weight during the first fortnight after delivery by about a pound and a half.

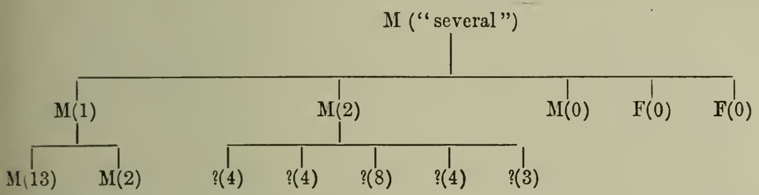
In chlorotic girls, Virchow pointed out that there is often hypoplasia of the aorta, but the relation between this condition and the anæmia is unknown.

(2) Some forms of atrophy must depend upon failure on the part of cells to assimilate nutriment. As Mott remarks, "a cell is not nourished but nourishes itself." We are here on somewhat uncertain ground, but we cannot otherwise fully explain many atrophies, especially those which show an inherited tendency.

Thus, senile atrophy has a marked tendency in different families to show itself abnormally early or abnormally late. During all periods of life, waste and repair go on side by side, but the relation between the two processes is different at different times. During growth, repair exceeds waste and the excess of nutriment is used in forming additional tissue cells, or in increasing the size of those already in existence ; during adult life, waste and repair are evenly balanced ; in old age, waste gains the upper hand. But it is not to deficient supply of nutriment that we must ascribe senile atrophy, for in most cases this does not differ greatly from the supply in adult life ; moreover, old age is exactly that period of life in which local growth of one organ—the prostate gland—is liable to occur, and old age is no barrier to the rapid growth of a malignant tumour. We must ascribe the peculiarity to the cell. We have examples in the opposite direction. The thymus gland atrophies—undergoes senile atrophy we may even say—at a period of life when growth elsewhere is at its height ; the generative organs, in woman, atrophy at a time when the body otherwise is almost in full vigour. One explanation—indefinite though it is—that we can give of all these facts is that the cells of each tissue inherit a certain span of life at birth of the individual. This span of life is transmitted through the generations of cells composing the tissue, but it loses in transmission. When it is nearing its end, the cells have become altered in such a way that they can no longer fully repair their waste, and therefore atrophy of the tissue sets in.

Sometimes the inherent defect of tissue nutrition involves a whole system and is very obvious. Thus, senile atrophy affects, amongst other tissues, the long bones, which in old age become thin, brittle, and liable to fracture spontaneously, or as the result of insignificant injury. But in certain families there is an inherited tendency to spontaneous fracture of bone, which is so marked as to force the conclusion that an hereditary fault in bone-formation and nutrition characterises the members of these families. Greenish relates a history of this kind, the genealogical tree of which is given below. Within brackets is placed the number of fractures that each individual sustained.

*Genealogical Tree of a Family showing great Tendency to Spontaneous Fracture of Bone (after Greenish).*



The inherited tendency to malformation of toes and fingers which is sometimes seen, and an example of which has been given in Chapter I., can only be explained on the assumption of an hereditary fault in the cellular processes going on at that time of intra-uterine life when the digits are being separated from the as yet undifferentiated extremity. And if we must accept the idea of an inherited peculiarity of cell arrangement, it is not unreasonable to accept also the idea of an inherited peculiarity of cell nutrition.

Other examples of atrophy which we must ascribe to inherited fault of cell nutrition are seen in Friedreich's paralysis, where the fault concerns nerve-cells, and in Duchenne's (pseudo-hypertrophic) paralysis, where it concerns voluntary muscle-cells. For these atrophies no other ætiological factor can at present be recognised than a hereditary one. In progressive muscular atrophy, a condition which, so far as the muscles are concerned, is anatomically very similar to Duchenne's paralysis, the muscular atrophy is secondary to changes in the spinal cord, and not primary.

In this connection it may be pointed out that conditions such as "writer's cramp," "hammerman's palsy," etc., generally end in atrophy of particular groups of muscles. In these "functional" diseases the first symptoms consist of spasmodic contraction, and the group of muscles affected is, in the large majority of cases, one that has for a considerable time been called into action in the pursuit of the patient's avocation. Whether the original seat of these conditions is in the nervous system or in the muscles affected is uncertain, but the whole series of changes from slight spasm to complete paralysis and atrophy seems to depend upon an impaired nutrition of cells due to over-stimulation. Probably, however, in these cases there is some inherent defect of nerve or muscle-cells which causes them readily to succumb to excessive stimulation; writer's cramp, for example, is a very rare condition considering the numbers that earn a living by the pen, but we should expect it to be relatively common, if excessive stimulation were its sole cause.

(3) Atrophy due to nervous causes is best seen in the case of muscles when some lesion has interfered with the integrity of their efferent nerve tract. But the interference must involve the lower segment of that tract. If we reduce an efferent tract to its schematic form it consists of an upper and a lower segment. The upper segment consists of a large ganglion cell in the cerebral cortex with its dendrites, that ramify locally and bring the cell into physiological connection with other cortical cells, and its axon, which travels by way of the internal capsule, crus cerebri, pons, and white matter of the cord down to a certain level, when it enters the grey matter, passes to the anterior horn and breaks up into a terminal arborisation. The lower segment is similar. It consists of a large ganglion cell in the anterior horn of the cord, with locally ramifying dendrites, and an axon which leaves the grey matter of the cord by an anterior nerve root and passes in a nerve trunk to a muscular fibre, where it breaks up into an arborisation. Connection, physiological if not anatomical ("synapsis"), is made between these two segments in the anterior horn of the cord, for the terminal arborisation of the upper segment is brought into close relation with the dendrites of the anterior cornual ganglion cell.

Now, when a muscle is paralysed, atrophy (in excess of that which is compatible with mere disuse) occurs only when the lower segment is affected. The upper segment may be involved so little that the change is not recognisable microscopically, and we have to assume that the lesion affects the communication between its terminal arborisation and the dendrites of the multipolar cell of the anterior horn; or it may be involved so considerably that it has degenerated over its whole length from grey matter of cortex to grey matter of cord; but though, in all the possible variations between these two conditions, there is paralysis, wasting of the involved muscle is never comparable with the marked atrophy that occurs when the lesion involves the lower segment in any part of its course. The excessive muscular wasting, for example, that occurs after section of an efferent nerve such as the ulnar, or when the ganglion cells in the anterior horns of the cord are affected by the changes constituting poliomyelitis, has no counterpart in the slight wasting that occurs when a limb is paralysed owing to some cerebral lesion. The ganglion cell of the anterior horn not only determines the nutrition of its own axon but also the nutrition of the muscular fibre with which the terminal arborisation of that axon is in apposition.

Similarly, the atrophy which occurs after section of all the nerves supplying a salivary gland is probably, in part, dependent upon removal of a trophic influence normally exerted upon the gland by the nervous system. How far atrophic changes in other glands are dependent upon, or independent of, primary nerve changes it is impossible to say.

Other well-marked examples of atrophy dependent upon nervous or upon nervous combined with vascular causes, are seen in facial and glossal hemiatrophy, in "glossy skin," and in scleroderma. Hemiatrophy of the tongue occurs when the hypoglossal nerve is interrupted in its course; this usually depends upon caries and necrosis of the upper cervical vertebræ or upon a nodule of new-growth, but in either case conductivity of the nerve is destroyed by pressure. The affected half of the tongue is flaccid, wrinkled, and greatly shrunken.

Glossy skin is seen on the hands after injury to the median or radial nerve, and shows itself as a marked thinning of the epidermis with disappearance of the normal furrows and striæ, the sweat-glands, and hair-sacs. A closely similar condition is often seen in the hands of patients suffering from rheumatoid arthritis, a disease which, according to some authors, is of nervous origin.

In scleroderma the corium takes on a leathery consistency; the disease may affect any part of the body, but it shows a predilection for the fingers. According to Lewin and Heller, who analysed over 400 recorded cases, the disease is an angeio-trophoneurosis. Some authors consider it to be a primary affection of the connective tissue for which no cause is known, but Lewin and Heller lay great stress upon the facts that in three cases one-half of the body was affected, in seven one-half of the face, and in twenty-one others there was a symmetrical arrangement of the scleroderma. These facts strongly suggest a nervous origin. The pathology of the affection is apparently as follows. First of all the blood-vessels are locally dilated and the temperature of the part rises, then follow changes in the vessel walls, including endarteritis. At first with the congestion there is œdema and overgrowth of the connective tissue of the skin, but finally, inflammatory and tropho-neurotic processes sharing in the work, the characteristic induration appears. The induration compresses the already modified blood-vessels and injures them yet more, the endarteritis advances, the blood-supply of the skin is more and more cut off, and ultimately the skin may be atrophied until it is no thicker than paper.

Just as a change in the spinal cord may determine atrophy of a limb, so removal of a limb may determine localised atrophy of the nervous system. Well-marked examples of such atrophy have been described in many cases in which amputation of a limb has been performed some years before death.

The atrophy affects the posterior column of the same side, the antero-lateral column of the opposite side, and the cortical centre normally concerned in voluntary movement of the limb. So, too, after enucleation of the eye in young animals there occurs atrophy of the anterior corpus quadrigeminum, optic thalamus, and occipital cortex. A closely similar condition is seen in the atrophy of one lateral lobe of the cerebellum, which has been found in association with atrophy of the opposite frontal convolutions.

*Changes undergone by a part during Atrophy.*—Atrophy may be uncomplicated, though this is rarely the case. Far more commonly it is associated with degeneration or infiltration processes, of which fatty degeneration and calcification are the chief. This is natural when we remember that all these processes agree in the fact that they are disturbances of cell nutrition on the way to cell death.

The converse proposition, that the degenerations and infiltrations are associated with atrophy, is even more true. Only in the case of extremely limited infiltrations is atrophy of cell protoplasm completely absent. Where the change is extensive, whether it be a degeneration or an infiltration, the cell protoplasm gradually disappears, commonly as the result of pressure atrophy. This is seen to a marked extent in a liver affected by the lardaceous change ; though the organ as a whole is enlarged, the hepatic cells are small and compressed, and in many places are completely wanting.

Atrophy of the proper cells of a tissue is often accompanied by overgrowth of its connective tissue. This combination is frequently seen in the kidney (interstitial fibrosis, "granular kidney") and in the liver (hepatic cirrhosis). In those cases it has been considered that the organ is affected with "chronic inflammation." It occurs in the atrophy of ovaries and testes after termination of sexual life, in scleroses of the nervous system, in fibroid "degeneration" of the heart and elsewhere. We shall return to the subject shortly.

Apart from the proliferation of connective tissue corpuscles seen in cases where atrophy is combined with connective tissue overgrowth, there sometimes occurs a proliferation of tissue cell nuclei. This is markedly the case in atrophy of muscle ; probably the changes here are comparable with the changes seen in the nuclei of leucocytes when they degenerate and become pus-cells. An explanation, however, of the fact is wanting, at least in the case of atrophic proliferation. Other changes, such as fibrillation in hyaline cartilage, disappearance of striation in voluntary muscle fibres, often precede or are early signs of atrophy; their meaning is unknown. In brown atrophy of the heart the atrophy is associated with the presence of pigment granules in the neighbourhood of the muscle nucleus; the pathology of this condition is unknown, but apparently it is a senile change.

When an organ or tissue commences to diminish in size there may at first be only a true atrophy, but very soon numerical atrophy is superadded, and it is with a combination of both processes that we have in most cases to deal. Agenesia is seen in its most marked form in certain congenital monstrosities. Intermediate conditions between agenesia and hypoplasia are not uncommon.

(ii.) **Hypertrophy.**—By hypertrophy is meant more than mere enlargement. A lung, the seat of croupous pneumonia, is enlarged, but it is not hypertrophied, a liver, the seat of carcinoma, is enlarged, but it is not hypertrophied. For the existence of hypertrophy not only must the tissue be larger than normal, it is necessary also that its structure should be normal. Strictly speaking this only occurs in hyperplasia; in the case of true hypertrophy the constituent cells differ from the normal though only in their greater size. Further, the term hypertrophy implies life; mere accumulation of dead material, *e.g.*, an uncut nail or excessive length of hair, is not hypertrophy.

A hypertrophied cell may be enormously enlarged; thus Kölliker found that the unstriped muscular cells of the uterus at the end of pregnancy are eleven times as long and four times as broad as normal. As a rule, however, the increase is not so great.

There is some difference of opinion as to how far hyperplasia conjoins with true hypertrophy in producing macroscopic hypertrophy. Thus, in cardiac hypertrophy, most authors believe that both conditions are present, but Tangl found by direct measurement that the muscle-cells are increased in diameter and that the mean diameter of the cells increases proportionately with the weight of the heart. He therefore maintains that the condition is one of true hypertrophy uncomplicated by hyperplasia, and in this view he is supported by some other authors. In the pregnant uterus hyperplasia certainly coincides with true hypertrophy; in the kidney, when there is compensatory hypertrophy, there is hyperplasia of the cells, true hypertrophy of the glomeruli;[1] but when fibrous tissue and epithelium increase in bulk they do so essentially by hyperplasia.

Hypertrophy involves tissues of widely different types: muscle, glandular elements, bone, epidermis, fibrous tissue. Often several of these are affected together; thus, when a voluntary muscle is hypertrophied, the inter-muscular fibrous tissue and the blood-vessels which it carries, and the bones at the points of muscular attachment, are hypertrophied also.

Hypertrophy may be, strictly speaking, either physiological or pathological. Nevertheless the "physiological" hypertrophy is very frequently met with under pathological conditions. Pathological hypertrophy is seen in such conditions as leucocythæmia, where the spleen is enormously enlarged, Hodgkin's disease (lymphadenoma), where lymphatic glands are enlarged, acromegaly,[2] leontiasis ossea (Virchow), pulmonary osteo-arthropathy (Marie), osteitis deformans, where bone is enlarged or thickened. Concerning the pathology of these conditions we are completely ignorant.

The two chief varieties of "physiological" hypertrophy with which we are concerned in pathology are "work" hypertrophy and "compensatory" hypertrophy. Work hypertrophy is seen in its simplest form when a muscular organ is called upon to overcome an increased resistance, as, for example, the urinary bladder when there is stricture of the urethra, the stomach when there is stricture of the pylorus, the voluntary muscles of an athlete. Such hypertrophy—at all events in the case of muscle—only occurs when the work to be done lies well within the reserve power of the tissue. It is an old experiment which shows that a loaded muscle contracts more forcibly with increase of the load up to, and only up to, a certain point; when the load is increased further, contractions diminish in force until at last they cease. It follows therefore, since functional activity and supply of nutriment by actively dilated blood-vessels go hand in hand, that increase beyond a certain point of the work to be done must of necessity lead, not to hypertrophy, but to atrophy and degeneration. And whether exercise of function be the *cause* of hypertrophy or no—a question to which we shall return shortly—there is no doubt that the two conditions accompany one another, so that hypertrophy can only occur when the work to be done is well within the reserve power of the tissue at the moment when it is called upon to perform that work. This is clearly seen in the case of the heart; a slight incompetence of the mitral valve leads to great hypertrophy of the left ventricular wall and little dilatation of the cavity, but a considerable incompetence, under similar circumstances, leads to great dilatation of the cavity and a thinning of the ventricular wall.

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[1] Eckhardt (*Virch. Arch.*, vol. cxiv., 1888, p. 217) believes that in compensatory hypertrophy of the kidney due to congenital absence of the other organ, there is hyperplasia and hypertrophy of both glomeruli and tubules; if the defect be acquired there is hypertrophy alone and no hyperplasia of either glomeruli or tubules.

[2] See Chap. XIII. Sect. vii.

Compensatory hypertrophy occurs in its simplest form where one of paired organs is absent or removed.[1] When one kidney is removed or destroyed experimentally, or in the course of disease, the other hypertrophies. Other examples of the kind are seen in the hypertrophy of lymph glands after excision of the spleen, hypertrophy of the remaining portion of a gland such as the liver or pancreas, when a portion has been extirpated; perhaps also in the hypertrophy of the pituitary body which has been found by some observers after thyroidectomy and in myxœdema.

Work hypertrophy and compensatory hypertrophy come close to one another, but apparently there is a difference between them. The hypertrophy seen in one kidney after removal of the other can easily be associated with increased work, for the body requires to rid itself of a certain amount of nitrogen, salts, and water, whether there be one kidney or two, and removal of one organ necessarily throws increased work upon the other. But in the case of the testis, so far as we know, no increased work is thrown upon the remaining organ if one of them fails to develop or is removed, and yet there is hypertrophy. We approach here the question whether nervous influences control growth as in some cases they control nutrition. The subject is a difficult one and cannot be discussed here, but that growth is in some cases independent of the nervous system, is shown conclusively by the facts that anencephalous and amyelous monsters show well-developed tissues in other respects, that epithelial structures (*e.g.*, hair, teeth) and even bone may develop in dermoid cysts, and in a most marked manner by the fact that in the embryo early growth and division of cells, and even the formation of the nervous system itself, are carried out independently of nervous control.

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[1] Not all cases of enlargement under these conditions are hypertrophic. Thus, when one lung has been destroyed by disease the other lung becomes enlarged, but it is not hypertrophied, for in the first place there is no evidence of new formation of lung tissue, and in the second place, the enlarged lung is not normal but emphysematous.

Hypertrophy being fundamentally growth carried beyond the normal limits, the conditions underlying hypertrophy are essentially those underlying normal growth. These are: (1) an inherent power of growth on the part of the cell; (2) an excessive supply of nutriment; (3) a stimulus.

Concerning the first two of these there is no doubt, though the hypertrophy of bone which is seen after prolonged administration of phosphorus, and the general increase in size and vigour (not confined to the skeleton) seen after prolonged administration of arsenic, have, by some authors, been considered to depend, not upon an excessive supply of nutriment, but upon a diminished tissue waste. But in the case of the stimulus there is great divergence of opinion. Cohnheim considered that the stimulus to increased growth is the increased amount of nutriment conveyed to the part by an active hyperæmia called forth by functional activity; no stimulus, whether nervous, mechanical, chemical, thermic, or inflammatory, was, in his opinion, an effective cause of hypertrophy, except by the way of active congestion. Ziegler holds that the stimulus for hypertrophy is increased work. Bizzozero divides tissues into three groups: (*a*) those whose cells proliferate without intermission so long as the individual lives—these he calls *labile* cells, and to them belong the cells of glands (*e.g.*, sebaceous) which break down into the secretion, skin, and its appendages; (*b*) tissues whose cells proliferate no more once they have gained their specific characters, which occurs at or soon after birth—these are *stable* cells, and to them belong bone, cartilage, smooth muscle and tissue of glands secreting amorphous substances; (*c*) tissues, the cells of which have ceased to proliferate during embryonic life, though differentiation of the tissue may not have taken place at that time—these are *permanent* cells, and of this kind are nerve and striated muscle-cells. He has shown through his pupils that congestion from vaso-motor paralysis (Morpurgo) or heating (Penzo) favours a proliferation of labile cells, but cannot start proliferation of either stable or permanent cells. Sacerdotti attaches himself to Ziegler's view, for he found in a dog, from which one kidney had been removed, that if he reduced the amount of material to be excreted by starving the animal, hypertrophy and cell-division were absent from the remaining kidney. He found further that if he injected into a normal dog once or twice daily for several days the blood of a bilaterally nephrectomised dog, that the kidneys of the normal dog showed numerous karyokinetic figures. Ribbert allows that increased functional activity and hypertrophy or hyperplasia are found together, but he doubts whether they stand to one another as cause and effect. He believes that the stimulus to increased growth is to be found in a mechanical effect of the hyperæmia. He holds that all cells have an inherent capacity for growth, in some cases greater, in some cases less, but that this inherent capacity is held in check by the "tissue-tension (*Gewebspannung*)" of neighbouring parts, and by the influence which the whole body exerts upon its component parts. When a tissue ceases to grow, this does not depend upon the fact that its capacity for growth is exhausted as Cohnheim held, but is due to the fact that tissue-tension has become sufficient to inhibit a manifestation of the inherent power of growth which still lurks in its component cells. Hence, when the tissue-tension is diminished, as it is when parts are separated from one another, *e.g.*, by hyperæmia, the inherent power of growth is no longer restrained, and therefore growth, *i.e.*, hypertrophy, takes place. This same explanation Ribbert applies to the processes of regeneration and repair, and, as we shall see later, in a slightly modified form to tumour and cyst-formation. · It must be noted that by "tissue-tension" Ribbert implies the sum of all the opposing influences acting upon a part, and not mechanical factors alone.

As to the mode in which growth takes place, it is held that true hypertrophy consists in separation of the molecules composing a cell protoplasm, and intercalation between them of new molecules of water and of protoplasm derived from the blood. This process, it is generally considered, depends upon osmosis or a process akin to osmosis. Thus Loeb, dealing with functional hypertrophy of muscle, says that, probably, as the result of functional activity, the osmotic pressure in the muscle bundles rises, and the number of molecules in solution in the muscle substance increases. The water entering the muscle by osmosis would increase the volume of the muscle and new molecules could be laid down in the enlarged spaces. He says that quite a small amount of muscular action raises the osmotic pressure of muscle by 50 per cent. Hyperplasia not only includes growth, but also cell division, whether direct (amitosis) or indirect (mitosis, karyokinesis). The phenomena observed when cells are dividing are of course well established, but little or nothing is known as to the factors upon which they depend other than those which apply to growth generally.

(iii.) **Fibrosis and Certain Allied Changes in Bone and Joints.**—We have already seen that in repair of composite tissues new formation of fibrous tissue is a very prominent factor. In chronically inflamed parts, therefore, the amount of fibrous tissue is often greatly increased. This fibrous tissue is true scar tissue. But besides cases of this kind, which are strictly inflammatory, an increase of fibrous tissue occurs under conditions where there is no evidence that inflammation is or has ever been a factor. Thus, in Duchenne's (pseudo-hypertrophic muscular) paralysis, the calves and buttocks are enormously increased in size, the increase being due solely to a hyperplasia of the inter-muscular connective tissue with a deposition in it of much fat. In chronic granular kidney, in cirrhosis of the liver, in fibroid disease of the heart, in sclerosis of the nervous system, there is a similar increase of fibrous tissue, and it may be so considerable that in places this is the only tissue recognisable.

Now, though the change in Duchenne's paralysis has never been regarded as inflammatory, and though in fibroid disease of the heart and sclerosis of nerve tracts there have always been some doubts on the point, in the cases of granular kidney and hepatic cirrhosis it was long held without question that the increased fibrous tissue is true scar tissue and that fibrosis of these organs is really the result of chronic interstitial inflammation. Hence granular kidney is at the present time often called *chronic interstitial* "*nephritis*," cirrhosis of the liver often regarded as a form of *chronic interstitial* "*hepatitis*," and (though less frequently than in former years) fibroid heart is sometimes termed a *chronic* "*myocarditis*," and sclerosis a *chronic* "*encephalitis*" or "*myelitis*."

But apart from the fallacy introduced by dividing inflammation into "interstitial" and "parenchymatous" and attaching the conditions under discussion to the "interstitial" variety, evidence that, in these cases, there has ever been inflammation in the accepted sense of the word, is meagre or entirely wanting, and is wholly unsatisfactory. Many authors, therefore, at the present day refuse to consider this kind of fibrous tissue-formation as inflammatory. They point out that almost all cases of atrophy are accompanied by a non-inflammatory hyperplasia of fibrous tissue. Thus it occurs in Duchenne's paralysis, in the post-natal or embryonic changes occurring in atrophy of the ductus venosus, urachus, ductus arteriosus, thymus, in atrophy of the ovaries and testes after termination of sexual life, and so on. Hence they conclude that in cerebral and spinal scleroses, in granular kidney, in cirrhosis of the liver, in fibrosis of the heart, and allied conditions of the same fibroid nature, the hyperplasia of connective tissue is compensatory to an antecedent disappearance of the proper cells of the tissue, and is not inflammatory at all.

For the strict proof of this proposition it is necessary to show that in granular kidney, etc., the true elements of the tissue are first of all affected by those agents which are commonly accepted as causes of the fibrotic change. In the case of fibrosis of the heart, it has been noted that the condition especially occurs along with changes in the coronary arteries or their branches, and these changes lead to impaired nutrition of the myocardium. Many investigators have sought to determine the point with reference to the liver and kidney (especially the former), working with alcohol, chloroform, ether, phosphorus, etc. Though there is divergence of result the balance of evidence goes to show that these agents act primarily on the cells, and that the fibrosis is secondary. In the case of sclerosis of the nervous system it has over and over again been shown experimentally that after degeneration of a tract, sclerosis gradually takes place, and that the connective tissue formed under these conditions is formed without the slightest trace of inflammation.

In the case of cirrhosis of the liver, the view that fibrosis is secondary has been supported by Wickham Legg, Charcot and Gombault, Ackermann, Hamilton, and many others. Afanassiew, working with alcohol, found that administration over long periods (rabbits, four months, dogs, nine months) leads to the formation of necrotic foci in the liver, which act as irritants to the surrounding tissue; this reacts by multiplication of connective tissue cells and formation of giant-cells, and ultimately the focus is replaced by fibrous tissue. Lafitte found in rabbits that alcohol directly affects the hepatic cell and leads to its atrophy. Mertens found in rabbits caused to live in an atmosphere containing vaporised alcohol, that the liver shows a marked increase of fibrous tissue if the animals live long enough (a year), and that in these cases the liver-cells are but slightly altered; when the animals succumb after a few months there is no increase of fibrous tissue, but the liver-cells are greatly degenerated. Adami notes that in cattle the infective disease known as "Pictou disease" is accompanied by a condition of the liver similar to that found in cirrhosis in man; probably in this case the irritant is a bacterial toxin which acts as a protoplasmic poison. Gerhardt found that, after ligature of the bile duct in rabbits, numerous necroses appear in the liver, which are afterwards replaced by newly-formed connective tissue.

On the other hand, von Kahlden was unable to find any cirrhotic modification in the livers of a variety of animals to which he gave alcohol, though he observed an intense hyperæmia. De Rechter, too, concluded, from numerous experiments on rabbits and dogs, that the hepatic cells remain absolutely intact, except for an atrophy undergone by reason of the compression to which they are subjected from contraction of the connective tissue which is newly formed in parts of the lobule.

It must be confessed, however, that even the most favourable of these experiments do not finally dispose of the question, for if the "necrosed foci," "degenerated cells," etc., act as "irritants," one might argue that they must cause inflammation, and therefore that the connective tissue produced, even though produced secondarily, is itself of an inflammatory nature. If we adopt Ribbert's theory of hypertrophy, the difficulty vanishes, for localised death of the cells must modify tissue-tension and set free the hitherto restrained capacity of growth of surrounding cells. That in this case it should be the connective tissue cells and not the hepatic cells which proliferate does not constitute a difficulty, for we have ample evidence that connective tissue can thrive under nutritive conditions which cause more delicate tissues to succumb. One argument against Ribbert's theory, it may be mentioned in passing, is that it affords so easy an explanation of so many processes; the more we learn of pathology, the more we find that very simple explanations are liable to be upset by later investigations.

Under this heading may also be mentioned certain morbid conditions of bones and joints in which it is questionable whether inflammation plays a part, though such is indicated by the names given to the affections. These are rhachitis (rickets), rheumatoid arthritis, osteitis deformans. With them may be placed osteomalacia, Charcot's "arthropathies" (seen in some diseases of the nervous system, especially tabes dorsalis), leontiasis ossea (Virchow), and perhaps acromegaly[1] and Marie's hypertrophic pulmonary osteo-arthropathy.

The pathology of these conditions is, in most cases, very obscure. They are nutritive disorders, whether purely atrophic (osteo-malacia), purely hypertrophic (leontiasis, acromegaly,[1] Marie's osteo-arthropathy), or a combination of atrophy in some places with hypertrophy in others (rickets, rheumatoid arthritis, osteitis deformans, Charcot's arthropathy). A few of these conditions will be examined more closely.

In osteo-malacia there is extreme thinning and softening of bones. The shafts of the femora, for example, may be no thicker than paper, the medullary canal has widened in diameter, and the bone may be so soft as readily to be indented with the finger-nail. The condition is largely, but not entirely, one of pregnant and suckling women; in cases where pregnancy and lactation are excluded, onset of the bone-condition has often been preceded by a period of nervous or mental depression. Levy made chemical examination of the femora in a well-marked case of osteo-malacia. He found that the mineral salts of the bone are diminished to about one-sixth of the normal, but that the proportions of phosphorus to lime and phosphates to carbonates are the same as in normal bone. It has been supposed, though on insufficient grounds, that osteo-malacia depends upon an excessive formation of lactic acid in the body which dissolves the inorganic constituents of bone. But apart from other objections to this view, Levy found that whereas normal bone, when immersed in 1 per cent. solution of lactic acid, loses more carbonate than phosphate, this is not the case in osteo-malacia. The process is not, therefore, a decalcification such as is seen in artificial decalcification of bone for histological purposes, but is a true converse of ossification and consists in the removal of molecules of phospho-carbonate as such.

Rickety manifestations are seen to the most marked extent at the growing ends of bones, where they consist in a hyperplasia and hyperæmia of periosteum, a hyperplasia of cartilage, an irregularity and greater width of the line of ossification, a removal of previously formed bone, and its replacement by irregular bone deficient in lime salts. But rickets does not only affect bones; liver, spleen, muscle, tendon, mucous membrane, skin, blood, all share in the disorder, and the frequency with which general convulsions, spasmodic contractions of muscle groups (as in tetany), laryngismus stridulus, occur in rickety children, shows that the nervous system is not exempt.

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[1] See also Chap. XIII. sect. vii.

There is overwhelming evidence that rickets must be connected ætiologically with deficient supply or assimilation of certain food-constituents. "The chief and constant defect appears to be an insufficient supply of animal fat, and therewith also, in certain cases, a deficiency of earthy salts in the form of phosphates; at the same time, if animal proteid be deficient, the disease is intensified" (Cheadle). As to the way in which these faults in diet produce rickets, it is impossible to speak. Deficient absorption of lime salts, excessive production of lactic acid, and many other suggestions have been made, but they are all more or less unsatisfactory. It is important to note, however, that semi-starvation does not lead to rickets; a half-starved child or animal is weak and puny, but it is not by any means necessarily rickety.

Rheumatoid arthritis and Charcot's arthropathy may be considered together, for the changes to which they lead are very similar, if not, in the early stages, quite identical. These changes affect joints and the bone in their neighbourhood. They consist in atrophy, degeneration and disappearance of articular cartilage, and, to a certain extent, of bone, together with a synchronous formation of new and dense bone in the immediate neighbourhood of the joint. The changes are like and yet unlike those seen in true inflammation of joints and bone, and it is here just as difficult to determine whether we are dealing with a chronic inflammation or not, as it was in the case of cirrhosis of the liver, chronic granular kidney, and those other conditions which we have determined to sum up under the name "chronic fibrosis."

In the case of Charcot's arthropathy, since the joint affection is undoubtedly associated with severe nervous lesions, it has been suggested that the change is "trophic," and evidence that the nervous system controls nutrition of joints. And in the case of rheumatoid arthritis, it is certain that depressing mental and bodily causes play an important part, while it is equally certain that those joints suffer earliest and most severely which have been constantly called into play by the patient's calling; in this respect the disease having much in common with such diseases as writer's cramp, hammerman's palsy, etc. So that the idea suggests itself that the joint and bone changes in rheumatoid arthritis may be "trophic" also in the same sense. But Shüller, Ballantyne, Wohlmann and Blaxall, and other authors, have described micro-organisms which they have found in the joints of patients suffering from rheumatoid arthritis, and which they regard as the cause of the disease, and it may well be that Charcot's arthropathy is induced by some irritant, whether bacterial or not, which would be without effect but for the relatively anæsthetic condition of the joint. It is impossible, therefore, to decide with certainty whether the two conditions are similar in pathology, or whether they are entirely different, and if similar, whether both are essentially "trophic" or both essentially inflammatory.[1]

In the case of Marie's osteo-arthropathy, so little is known concerning the condition, that we are not yet in a position to discuss its pathology; Marie conjectures that the condition is caused by absorption of some toxic substance from diseased pulmonary tissues, Thorburn, that it is really tubercular. Leontiasis ossea and osteitis deformans are equally obscure in pathology. Acromegaly will be considered later and in connection with the internal secretions; in this disease the pituitary body is almost always found to be altered.

In many of the conditions of bones and joints that have been mentioned here, it will be noted that structural or functional modification of nerve-matter is present. Whether it will ultimately be shown that all these conditions are "trophic" in the sense that they immediately depend upon some derangement in nutrition brought about by way of the nervous system, it is impossible to say. The important point to remember is that they bear closer relationship to the nutritive disorders, necrosis, degeneration, atrophy, hypertrophy, than they do to true inflammation. True inflammation of bones and of joints is known, both in the acute and in the chronic form, but there are wide differences between even the most chronic inflammation of a bone or joint and the conditions discussed above.

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[1] In a discussion upon the subject of Rheumatoid Arthritis at the Montreal meeting of the British Medical Association (reported in *Brit. Med. Journ.*, Oct. 30, 1897), Stewart remarked that "evidence pointing to a nervous origin of rheumatoid arthritis is very meagre," and quoted Baümler as saying that there is "not sufficient evidence to support the views commonly held as to the nervous origin of rheumatoid arthritis." But granting the justice of these criticisms, they may equally well be applied to any other view with regard to the ætiology of the disease, and, in my opinion, with even more force.

V. **The New-growths.**—(i.) **Definition.**—Though it is impossible to frame a definition of the new-growths which shall be above criticism, a definition of some kind is convenient; we shall adopt that of Ziegler. "A neoplasm or tumour is a new formation of tissue which is atypical in structure, which subserves no useful purpose to the whole economy, and the growth of which has no typical termination."

In this definition the expression "new formation of tissue" excludes formations such as "retention" and "exudation" cysts, which are "swellings," and therefore etymologically should be included amongst the tumours, but which are by most authors excluded from the group. Insertion of the attribute "atypical" eliminates the generalised, but not the localised, hypertrophies, for these latter may under certain circumstances constitute true tumours. The fact that a new-growth "subserves no useful purpose" is of great importance, not only by reason of the direct statement itself, but because it makes certain further exclusions: it excludes, for example, from the tumours, provisional callus formed during repair of the bone, however voluminous. And lastly, the statement that the growth of a tumour has no "typical termination" suffices to separate the tumours from all swellings of inflammatory origin and especially from the "infective granulomata" or "infective tumours" (Cohnheim) which are tumour-like but are built up of granulation tissue and are therefore "inflammatory."

(ii.) **Modes of Classification.**—Virchow divided the new-growths into three classes, histioid, organoid, teratoid. The histioid tumours corresponded with one simple histological tissue; organoid tumours had a more complicated structure, being built up of several types of tissue—in a modified sense they corresponded to definite organs of the body; teratoid tumours were still more complicated in that they were built up of whole systems of tissues, though imperfectly developed. The class of teratoid tumours is still recognised: it is made up by the "dermoid cysts." Use of the terms "histioid" and "organoid" has, however, largely been discontinued, because Virchow's distinction between the two classes of tumour is not a real one—the simplest fibroma is complex in that it contains some blood-vessels besides its constituent fibrous tissue.

New-growths have also been described as "homologous" and "heterologous." By these terms are meant, respectively, conditions in which a tumour occurs in tissue of like kind with itself, or occurs in a tissue unlike itself; thus a fibroma growing from tendon is homologous, an enchondroma growing in the parotid gland or testis is heterologous.

Far more important is the division of tumours into two great classes according as they arise from (*a*) mesoblastic, or (*b*) epi- or hypoblastic structures; for it is found that certain characteristics distinguish the two groups. Better perhaps than this division, owing to the present uncertainty with regard to the embryological origin of many structures of the body, is a distinction of tumours into those of the connective tissue type and those of the epithelial type. Though such a division does not include a few varieties of tumour it embraces the great majority.

Lastly, the clinician has divided the new-growths into non-malignant[1] and malignant, a mode of separation of vast practical importance. The criteria of malignancy are essentially two: (1) tendency to spread locally, (2) tendency to form metastases or secondary growths at a distance. From these criteria follow other characteristics of the two groups.

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[1] Non-malignant growths are sometimes spoken of as "benign" or "innocent." But to call any pathological condition "benign" is the height of euphemism, and to call a tumour "innocent" when it may lead to death owing to the pressure which it exerts, or because it takes on malignant characteristics, is at least optimistic.

(*a*) The non-malignant tumours are encapsulated, the malignant tumours have no capsule. This statement is generally true, but there are certain exceptions: a fatty tumour, for example, is essentially non-malignant, but it is not invariably circumscribed, "diffuse" lipomata being known.

(*b*) The non-malignant tumours grow slowly, the malignant tumours grow rapidly. This statement again is only generally true: it depends upon the relative richness in cells; a scirrhus of the breast, though undoubtedly malignant, grows slowly and may never reach any considerable size. The slowness of growth in the case of non-malignant tumours is the chief cause of their encapsulation, and the more slowly the tumour grows the more dense its capsule.

(*c*) The non-malignant tumours do not recur after removal, the malignant tumours tend to recur locally. These characteristics obviously depend upon the question whether the growth is circumscribed or not, for local recurrence after removal simply means that a portion of the growth has been left behind. Complete removal of a non-malignant fibro-adenoma of the breast is easily possible, whereas a malignant growth in the same gland extends far beyond the obvious limits.

(*d*) Non-malignant growths are usually single, malignant growths usually multiple. This depends upon the fact that malignant growths form metastases. Nevertheless, here again we meet with exceptions; cutaneous fibromata, exostoses, uterine fibro-myomata are non-malignant growths and yet they are frequently—even generally—multiple, whereas "rodent cancer" is only locally malignant and therefore is single, and the myeloid sarcomata but rarely form secondary growths. When non-malignant tumours are multiple, they only involve one system of tissue; thus in the examples given above they affect true skin, bone, uterine muscle respectively; this is not the case with the malignant tumours.

(*e*) Non-malignant tumours do not endanger life except by reason of their size and pressure effects, malignant tumours disturb general health and ultimately lead to death. These characteristics depend upon several factors. The non-malignant tumour displaces tissues, and such destruction as occurs is due to a pressure atrophy which is relatively slow because growth of the tumour is relatively slow. The malignant tumour, on the other hand, by its relatively rapid growth, leads to a greater destruction of tissue locally, and to a greater extent deprives other tissues of nutriment owing to the amount which it diverts for its own use. Important in this connection is the observation of Brault. He found that the amount of glycogen present in a tumour stands in direct ratio to the rapidity of its growth, so that soft and cellular tumours are very rich in glycogen. In the case of a large tumour, he found that the percentage amount of glycogen far exceeded the amount present in the liver of animals or of criminals killed in full digestion, and was only comparable with the amount present in the tissues in the early days of fœtal life. It is possible, too, that the metabolic products of malignant growths may be deleterious to the body, though of this we have at present no evidence; reference here is, of course, not made to absorption of toxic substances formed during putrefaction of portions of the new-growth.

(iii.) **Histological Characters of New-growths.**—The non-malignant tumours are all composed of tissues for which some counterpart exists in normal extra-uterine life. They may be built up of elements belonging to the connective tissues (or more accurately of mesoblastic elements) alone, or epithelial elements may enter into and form a fundamental portion of their constitution. Thus we may have a tumour formed of fibrous tissue (fibroma), of cartilage (chondroma, enchondroma), of bone (osteoma, exostosis), of fibrous tissue containing fat (lipoma), of mucoid tissue similar to the Whartonian jelly of the umbilical cord (myxoma), of blood-vessels (angeioma), of lymphatics (lymphangeioma), of neuroglia (glioma). We may have a tumour formed of unstriped muscle fibres (leiomyoma), or of striated muscle fibre (rhabdomyoma), of nerves (neuroma[1]).

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[1] Most neuromata are falsely so-called, being really nothing but fibromata involving nerve trunks; in rare instances true neuromata are found. The best

From all of these epithelial elements are absent. Then we may have tumours mainly consisting of heaped-up, hardened and altered epidermal cells (keratoma, cutaneous horns), or tumours into the composition of which fibrous tissue and epithelial cells enter. Here the epithelium may be squamous (cutaneous papilloma or wart), columnar (as in rectal and other intestinal polypi), or spheroidal (adenoma). In all these cases the constituent elements resemble more or less closely the same elements in the normal extra-uterine body.

The malignant tumours, on the other hand, are composed of cells for which the counterpart exists in embryonic life alone. Here again they may be built up of elements belonging to the connective tissue group (sarcoma, endothelioma), or may be composed mainly, though not entirely, of epithelium (carcinoma, true cancers).

Sarcomata are described, according to the shape of the cells composing them, as large or small round-cell sarcomata, large or small spindle-cell sarcomata, oat-cell sarcoma, mixed-cell sarcoma. Sarcomata, in which giant-cells are present, are known as myeloid sarcomata, those in which the constituent cells or some of them contain pigment are known as melanotic sarcomata. *Cæteris paribus*, the smaller the cell, the more malignant the growth, and *vice versa*. Exception, however, must always be made of the melanotic sarcoma, for whether composed of large or of small cells, its malignancy is intense, owing to the rapidity with which secondary growths occur in this variety; locally they are far less malignant than many other varieties of sarcoma. Since a sarcoma cell is essentially a cell belonging to the connective tissue group, it forms or tends to form a tissue which shall lie between the individual cells, whether that be fibrous tissue, cartilage, or bone. This constitutes an essential difference between the sarcomata and the carcinomata; for in the carcinomata no intervening substance is present between the constituent epithelial cells. In this respect endotheliomata hold a unique position, for though they are generally classed with the sarcomata

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examples of true neuromata occur in the bulbous enlargements of nerves seen in an amputation stump.

in accordance with the belief that they are of mesoblastic origin, they show no inter-cellular substance, and therefore resemble, in this point, the carcinomata.

Carcinomata are described according to the character of the epithelial cells of which they are composed. Thus we meet with squamous cell carcinoma or epithelioma, columnar cell carcinoma or epithelioma, spheroidal cell carcinoma or malignant adenoma. According to the primary seat of the carcinoma, so will be the nature of the epithelium of which it is composed; a carcinoma of the lip or anus is squamous cell epithelioma, of the intestine is columnar cell epithelioma, of the breast (if it involves the true gland substance) is spheroidal cell carcinoma.

The new-growths show many intermediate forms. Thus a leiomyoma is never composed of unstriped muscle fibres alone, a certain amount of fibrous tissue is always present, and in some cases it may preponderate to so great an extent, that the clinical term "uterine fibroid" is amply justified. Intermediate forms are known as fibro-myomata. So, too, we have fibro-adenoma, lipo-myxoma, myxo-chondroma, fibro-myxo-chondro-adenoma (parotidean tumour), etc.; indeed it is far more common to meet with compound forms than with simple forms of tumour. We shall not enter into the vexed question whether tumours exist midway between the sarcomata and carcinomata ("*sarcoma carcinomatodes*," "*carcinoma sarcomatodes*").

When a non-malignant tumour becomes malignant, it maintains its essential type. Thus a fibroma becomes sarcomatous not carcinomatous, a papilloma becomes carcinomatous not sarcomatous, a non-malignant adenoma of the breast becomes a carcinoma of the breast and not a sarcoma. This rule is strict, and apparent exceptions may generally be explained. This "breeding true" of the tumours is even better seen in the case of metastatic growths; if a squamous cell carcinoma forms secondary growths in the liver, squamous cells are found in the hepatic nodules and not spheroidal cells; similarly, if a columnar cell carcinoma forms secondary growths in the liver, columnar cells are found in the hepatic nodules. So also if a myeloid sarcoma forms secondary growths in the heart, giant-cells occur here as in the primary tumour. Nevertheless, in the case of sarcomata, differences referrible to the rate of growth may be observed; thus the primary growth may consist of large spindle cells, secondary growths of small spindle, or even round, cells. But when the primary growth consists of small cells, secondary growths never consist of large cells, nor if the primary growth consists of round cells are secondary growths ever found to consist of spindle cells.

(iv.) **Nutritional Changes undergone by New-growths.**—The new-growths are very liable to undergo certain of the nutritive changes that have already been described in this chapter. Thus, the cells may undergo atrophy, fatty degeneration or colloid change, the stroma may undergo the mucoid change, or parts of the whole tumour may undergo local necrosis with disintegration (ulceration), or calcification. These changes principally affect the central portions of a growth, owing to its more limited blood-supply, but ulceration, of course, implies a superficial change, and occurs when the new-growth has involved either the skin or a mucous membrane.

Atrophy of cells is well seen in the case of a hard cancer of the breast (scirrhus). The fibrous tissue which surrounds the masses of (cancerous) epithelial cells, increases in density, contracts, and causes pressure atrophy of the cells, with the result that, however cellular the peripheral portions of such a cancer may be, and however cellular the central portion may originally have been, the central portion ultimately comes to consist of little more than dense fibrous tissue. The colloid change is chiefly seen in carcinoma of the stomach and the peritoneum; as a rule the change occurs so rapidly that it is present in the peripheral portions of the tumour as well as in the central portions. The colloid change being one that affects epithelium it is of course absent from the sarcomata, in this respect differing from the mucoid change which affects connective tissues and their cells, and which therefore is especially liable to occur in sarcomata. Calcification occurs principally in hard fibromata, and especially in fibro-myomata of the uterus; so great an amount of the calcium salts may be deposited in a uterine fibroid that it is quite impossible to cut it with a knife. An important change of a different kind, but one that may be mentioned here, is that brought about by hæmorrhage. In any rapidly growing tumour, but especially in the soft sarcomata owing to the embryonic characters of their blood-vessels, hæmorrhage may occur. As a result the tumour may be converted into a fluctuating swelling which at times it is impossible to distinguish macroscopically from a true hæmatoma or blood-cyst.

This brief exposition of the characters of new-growths must suffice. We must now turn to their pathogenesis and shall at once note a difference. For whereas much is known concerning the pathological anatomy and the clinical characters of the new-growths, nothing is known with certainty concerning their pathogenesis. At present we are obliged to content ourselves with theories.

(v.) **Pathogenesis of the New-growths.**—Leaving on one side theories which referred the ætiology of tumours to such vague conditions as morbid states of the blood, etc., we have to consider six distinct hypotheses that have been put forward to explain the pathogenesis of new-growths. They may be shortly described by the following titles:—

1. The theory of spermatic influence.
2. The theory of traumatic causation or causation by mechanical irritants.
3. The theory of embryonic remnants (Cohnheim).
4. The parasitic or infective theory.
5. The theory of anaplasia (Hansemann).
6. The theory of growth-liberation (Ribbert).

(1) *Theory of Spermatic Influence.*—By this theory it was assumed that the normal tissue of a part in which a growth occurs has become directly converted into the tissue of the tumour. Here we have an extension of the process known as "metaplasia" or conversion of one kind of cell into another. But the extension is unwarrantable. It is true that cells of a columnar epithelium may, if exposed to irritation, take on characters very similar to those of squamous cells; this occurs,

for example, when the uterus becomes inverted and prolapsed into the vagina. It is true that cartilage or fibrous tissue may become converted, on the one hand, into mucoid tissue, or, on the other hand, into a tissue more or less closely resembling true bone. But these are the limits of metaplasia, and there is not the slightest evidence that an epithelial cell, for example, can become converted into a connective tissue cell, or a connective tissue cell into an epithelial cell. In fact there is the strongest evidence to the contrary.

But even if we were able to grant this proposition, we should only thus be able to explain the extension of a new-growth; we should still be ignorant as to the origin of the first cells which exerted the spermatic influence. Here the theory of spermatic influence leaves us helpless.

(2) *Theory of Traumatic Causation or Causation by Mechanical Irritation.*—This theory is highly important; to it Virchow gives the greatest measure of his support. It makes use of the fact that new-growths are known to supervene in parts which have previously been subjected to injury or chronic irritation. The observations upon which it is founded may be illustrated by the following examples. Chronic irritation occurring in healing of a wound by second intention may lead to the appearance of multiple fibromata; neuromata are commonly seen on the ends of nerves involved in an amputation stump; chimney-sweeps sometimes suffer from scrotal cancer owing to chronic irritation of the parts about the groin by soot; workers with paraffin and tar suffer from epithelioma on the arms; cancer is liable to affect such parts as the lip in persons who habitually smoke clay pipes, and the tongue, when it has been irritated or lacerated by a broken or jagged tooth; cancer is liable to affect the breast, the œsophagus where it is crossed by the bronchus, the cardiac and pyloric ends of the stomach, the lower end of the rectum, all of which are regions especially liable to chronic irritation.

Cohnheim criticised this theory very severely, and in some respects unjustly. He rightly pointed out that a previous history of injury can only be obtained in about 14 per cent. of cases in which new-growths exist, and that this tacitly implies that in 86 per cent. of cases no injury can be inculpated. Moreover, if cases in which injury has been received were taken as the basis of calculation, the number in which that injury has been followed by a new-growth would form a much smaller percentage. His criticisms were fair, that new-growths are very uncommon on the hands and feet, which are parts extremely liable to injury, and that in the case of the breast, the nipple, which is much exposed to injury, is a rare seat of new-growth, whereas the gland itself, which is less exposed to injury, is frequently affected. But, on the other hand, he can hardly be held justified in denying, as he does, that neuromata after amputation, that scrotal cancer and the epithelioma of workers in paraffin and tar, that the epithelioma which develops sometimes at the base and out of a chronic ulcer, are true tumours, and in brushing aside the undoubted support which they give to the theory of mechanical irritation.

Nevertheless, it must not be forgotten that local traumatism and mechanical irritation may not be ætiological factors, but powerful adjuvant factors. This is the view which is generally held at the present day.

(3) *Theory of Embryonic Remnants.*—There is no more fascinating chapter in Cohnheim's *Lectures on General Pathology* than that in which he unfolds his doctrine of embryonic remnants for the explanation of new-growths. Cohnheim assumed that, "in an early stage of embryonic development, more cells are produced than are required for building up the part concerned, so that there remains unappropriated a quantity of cells—it may be very few in number—which, *owing to their embryonic character*, are endowed with a marked capacity for proliferation." By this assumption he explained the hereditary transmission of new-growths, the congenital appearance or appearance in the first years of life of some kinds of tumour, the atypical structure of new-growths, their absence of function, their persistence, the seats at which many of them are found. He explained thereby the fact that tumours may consist of any kind of tissue, in any degree of complexity. For according to the earliness or lateness in embryonic life at which the "remnant"

was formed, and according to its complexity, so the resulting tumour will be less differentiated or more differentiated, will more resemble embryonic or post-embryonic tissue in its structure, will possess a greater or a less tendency to rapid proliferation of cells.

Assuming the validity of his hypothesis that embryonic remnants exist, Cohnheim found no difficulty in understanding that, in most instances, they do not take on growth, *i.e.*, tumours do not form, till a later period in life. For he pointed out that in the generative organs, though the capacity for growth must be present in the cells, growth lags behind general growth of the body until it bursts forth at puberty. In the uterus particularly, the inherent capacity for growth may lie dormant during the whole period of sexual life, if the physiological stimulus of an impregnated ovum be not given, and yet the capacity for rapid growth resides in the cells none the less.

Given the existence of an embryonic remnant, some stimulus is necessary for the occurrence of cell proliferation. Here Cohnheim allowed that trauma or mechanical irritation may play a part in the causation of tumours by leading to that adequate blood-supply which is always necessary to growth. The dependence of growth in these embryonic remnants upon adequate blood-supply Cohnheim illustrated by the tendency of a tumour to take on sudden and rapid growth when the tissue in which it lies is supplied with an increased amount of blood for some physiological end. Thus, he alluded to the rapid growth of ovarian, uterine and mammary tumours during pregnancy, and to the frequent occurrence of exostoses during childhood when the bones are rapidly growing.

Cohnheim claimed an especial support for his theory, from the seats at which epithelial tumours (carcinomata) are liable to be found. He pointed out that they evince a special disposition to attack "the orifices of the body, the lips and tongue, alæ nasi and eyelids, the prepuce and glans penis, and the rectum; in addition the external os uteri is very frequently the seat of a cancerous tumour, while that portion of the œsophagus crossed by the bronchus is more liable to cancroid than are its other parts." These facts, which Virchow explained on the theory of mechanical irritation, Cohnheim claimed as supporting his theory, for "the above-named localities are most of them the seat, at some stage or other of embryonic development, of a certain complication. There occurs at the various orifices either a prolongation of the epiblast inwards or a conjunction between it and another epithelial tube or the like; and during this process some slight irregularity may, I think, easily happen which would give rise to a group of superfluous epithelial cells—that is, to the rudiment of a tumour." The peculiar localisation of epithelioma in the œsophagus he ascribed to the fact that "the œsophagus and bronchus were originally here united, so as to give rise to a developmental complication." Cancer of the rectum, he pointed out, develops not at the anus itself but higher up, where "the epithelial tube formed by the hinder portion of the gut unites with the anal invagination of the epiblast." In the case of the female generative organs, it is not the vulva which is most exposed to injury, that is the favourite seat of cancer, but the region in which "the pavement epithelium of the sinus urogenitalis coalesces with the cylindrical epithelium of Müller's ducts, viz., the orificium externum uteri." So also he ascribed the extreme frequency with which cancer affects the cardiac and pyloric ends of the stomach to "embryological complications, the occurrence of which is sufficiently indicated by the alteration of the epithelium at the cardia, at the pylorus, and at the junction of the portio pylorica with the fundus."

Now there have been raised four principal objections to Cohnheim's theory. The first objection is that primary growths are extremely rare in many regions, such as the nervous system, heart, kidney, the embryological development of which is highly complicated. This criticism is as just as was Cohnheim's criticism of the traumatic theory that a history of previous injury fails in 86 per cent. of cases. The second objection is that epithelial remnants are often found in the form of "epithelial pearls" in the tonsils and neighbouring parts in healthy individuals, and yet these parts are but rarely the seat of carcinoma. The validity of this criticism is not fully done away with, even though it be recognised that Cohnheim expressly implies that, for the development of a tumour from an embryonic remnant, it is necessary that the physiological capacity for resistance of the surrounding tissues should be reduced. The third objection is that Cohnheim separates from the true tumours epithelial growths such as are sometimes seen in ulcers or on scars. Neither histologically nor clinically can an epithelioma in one of these situations be distinguished from cases of epithelioma in which Cohnheim would have allowed the existence of embryonic remnants. His separation of neuromata and fibromata formed in the neighbourhood of an amputation joint from the true tumours comes into the same category. The fourth objection is that Cohnheim forced the teratomata and many of the cysts into an unnatural position in order to strengthen his hypothesis. These growths cannot fairly be included amongst the true tumours.

But in spite of these objections to the theory of embryonic remnants as an exclusive theory, it may fairly be accepted as an explanation of some kinds of tumour. The chief of these are enchondromata arising from aberrant groups of cartilage cells in ossified bone, tumours of parotid gland and testis, which also contain cartilage, adenomata arising from the postanal gut, melanotic sarcomata arising from congenital pigmented moles, rhabdomyoma of the kidney, and some others. In the case of dermoid cysts it is a highly satisfactory explanation, and the same is true, as we shall see, of many other kinds of cysts.

(4) *The Parasitic or Infective Theory.*—In a general form this theory was put forward many years before the modern view of infectivity was adopted. Hence, originally, the theory was not bound up with the idea of a microbial origin for any of the tumours. But recently it has assumed a great importance, owing to the fact that certain authors have brought forward evidence which they maintain points to microbial origins for carcinoma and sarcoma.

This theory is really concerned only with a portion of the new-growths, viz., those which form metastases; it therefore aims essentially at an explanation of the carcinomata and sarcomata. The basis of its adoption is the close similarity between the clinical characters of a case of malignant new-growth and a case of a certainly infective disease such as tuberculosis. Thus a local tuberculosis at the apex of one lung leads to secondary infection of the nearest (bronchial) lymphatic glands by way of the lymphatics, which may themselves show tubercular nodules, and if material from the primary, or one of the secondary, foci gains entrance to the blood-vessels and is carried away in the circulation, it leads, by the production of minute embolisms, to a generalised miliary tuberculosis. In the case of carcinoma there is also a local primary focus, the nearest lymphatic glands also become involved early, the lymphatics running from the primary focus to these glands may present chains of cancerous nodules, and a generalised carcinomatosis may occur. Carcinoma travels principally by lymphatics, sarcoma is disseminated by the blood-stream, hence generalised sarcomatosis is more common than generalised carcinomatosis; but that carcinoma may also travel by the blood-stream is shown by the fact that, when the stomach or intestine is the seat of cancer, the liver is always found to be secondarily involved.

Another point of resemblance exists in the histological similarity of many sarcomata to "inflammatory tissue" and particularly to granulation tissue. Every pathologist can point to many specimens in which diagnosis between the two kinds of tissue from microscopical sections alone is impossible. That this should be so is not surprising, for a sarcoma is embryonic connective tissue, and granulation tissue is nothing more, apart from its inherent tendency to become fully formed fibrous tissue, a property which is absent from the sarcoma.

But there are two important points of difference between the malignant new-growths and a certainly infective disease such as tuberculosis.

In the first place, tuberculosis can readily be conveyed from animal to animal though of a different species, but transmission of new-growths from man to lower animals has never been observed with certainty, and in the few instances of transmission in the lower animals that have been recorded, success has only attended inoculation of material from one member to another of the same species. In man, examples of carcinomatous auto-inoculation are common. In a case of uterine cancer, if the lower end of the great omentum reach down to the uterus, it will show nodules of cancer on its lower margin; auto-inoculation of cancer from one labium to the other, from the stomach to the colon, from the peritoneal surface of one portion of bowel to another, is frequently met with. But facts such as these do not prove that cancer is an infective disease, for they are quite comparable with the phenomena seen in "grafts" of epithelium, a case in which infectivity is out of the question.

The best examples of transmission from animal to animal are those recorded by Hanau and by Moran. Hanau successfully engrafted squamous cell carcinoma from the vulva of a rat into the peritoneal cavity of other rats. In one case, where death ensued after three months, the abdominal cavity was filled with nodules which presented the typical appearance of squamous cell carcinoma. Moran succeeded in transmitting an adenomatous growth from one white mouse to numerous other white mice. The primary tumour was found accidentally in the axilla of the first mouse, was removed aseptically, minced and injected subcutaneously into descendants of this mouse and into other mice. After a lapse of three months, and especially in descendants of the first mouse, tumours of purely epithelial, often papillary, structure showed themselves. These tumours grew to a large size, caused metastases, and produced death with considerable wasting. Inoculation of the substance into other species of animal, however, gave negative results.

In the case of sarcoma, the matter is even more difficult, owing to the similarity between sarcoma tissue and inflammatory tissue; hence it is doubtful whether the peculiar growths seen on the generative organs of bull-dogs and bull-bitches, which are transmitted from male to female and female to male, are sarcomata, or only special forms of granulation tissue.[1] Macroscopically, they present considerable resemblances to the sarcomata, and microscopically, the two cases that I have examined have been indistinguishable from round-cell sarcomata; but on the other hand, an absence of metastases argued strongly against the view that they were true sarcomata.

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[1] On this point see a paper by WASHBOURN, *Journ. of Path. and Bact.*, Jan. 1898.

In the second place, the constitutions of the primary and the metastatic growths are different in the cases of such a certainly infective disease as tuberculosis and the new-growths. For though the secondary tubercular nodule resembles the primary nodule in all its essential respects, and the secondary cancerous or sarcomatous nodule resembles the primary focus in the same way, the constitution of those nodules, whether primary or secondary, is fundamentally different in the two diseases.

This is best seen if we compare tuberculosis with carcinoma of a highly distinctive kind, say, squamous cell epithelioma. If we inject a culture of *B. tuberculosis* into the circulation of an animal, and the experiment is successful, we find that tubercular nodules are formed in the liver and elsewhere. Now the bacillus has led to the formation of the tubercle from the tissues which immediately surround it; the giant-cell, the epithelioid cells, the lymphoid cells, are derived from the pre-existing tissues of the part (connective tissue) or from wandering cells conveyed thither by the blood. That is to say, the tubercular nodule is essentially a modification of the normal tissue induced by the tubercle bacillus. But the case of squamous cell epithelioma is different, for here it is not a modification of the normal tissue which leads to the production of a nodule in the liver, but actual growth *in situ* of squamous epithelium itself. This is proved conclusively by the existence of numerous "epithelial pearls," for it is inconceivable that any constituent of the liver should actually become converted into squamous epithelium. A strict analogy to this condition is only seen in the case of tuberculosis in multiplication of the bacilli themselves in a metastasis, and that quite apart from the changes which the bacilli induce in the surrounding tissues. Exactly the same difference obtains if we compare tuberculosis with such a form of sarcoma as the chondro-sarcoma, for the metastases in the latter case, wherever they are situated, contain cartilage. In a word, secondary nodules in tuberculosis are *similar* to the primary nodule, because of the similarity in structure of the tissues in which the irritant is placed, the secondary nodules in carcinoma and sarcoma are *identical* in structure with the primary growth because, strictly speaking, they are parts of the primary growth. We shall return to this point later.

Now, impressed with the similarities between the clinical histories of the malignant new-growths and many of the infective diseases, numbers of investigators have endeavoured to find an infective agent or infective agents for the carcinomata and the sarcomata.[1] In this respect more attention has been given to the carcinomata than to the sarcomata, because of certain microscopic appearances often presented by cells of the former class of growth. It will suffice here to state that those authors who maintain the infective nature of cancer find, in the microscopic appearances alluded to, evidence of an animal parasite—a protozoon.[2] This conclusion is, however, denied by,

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[1] It is impossible to refer here to all these researches. Those who are especially interested in the subject will find an exhaustive summary by Strœbe (*Centralbl. f. Allg. Path.*, etc., vol. v., 1894, pp. 11, 60, 107), and critical discussions of the whole question of "cancer parasites" in Klein's *Micro-organisms and Disease*, p. 509 *et seq.*, and in the article by Shattock and Ballance in Allbutt's *System of Medicine*, vol. i. p. 206 *et seq.*

[2] Rüffer has reduced the hypothetical cancer parasite to a very few definite forms with which Shattock and Ballance agree. As seen in the protoplasm of the epithelial cells of the growing edge, say, of a mammary scirrhus, the fully-grown parasite consists essentially, according to Rüffer,

(1) Of a central round, oval, or slightly irregular nucleus, sometimes connected by fine delicate rays with the periphery.

(2) Of a variable amount of surrounding protoplasm, almost, if not quite, filling a capsule (now and then the protoplasm exhibits a series of peripheral granules).

(3) Of a doubly contoured capsule confining the whole.

Klein cannot accept these appearances as certainly indicating the presence of a parasite. Though he holds an open mind, he has himself seen on one occasion bodies like those described by Korotneff under the name of *Rophalocephalus carcinomatosus.* Korotneff (whose observations have been confirmed by Kurloff) described a pedunculated and band-like protoplasmic mass consisting of a spheroidal "head," and directly continued from it a band-like longer or shorter protoplasmic mass. The whole is without a sheath, and is situated partly within, partly without the epithelial cells of the cancer; the band-like stalk is several times the diameter of the individual epithelial cells. Their appearance is therefore quite unlike that of epithelial or other cells in a cancer. Korotneff has found these bodies in a variety of cancers, and he, Kurloff, and Klein all agree that perhaps, a larger number of investigators, who maintain that the microscopic appearances in question are due to agglomerations of chromatin, to vacuolated epithelial cells containing leucocytes, to cell invaginations, to degenerated epithelial cells or leucocytes, in fact to almost any condition excepting that of a protozoon. In the case of sarcomata, animal parasites are not inculpated, but Sanfelice, Roncali, Aievoli, Curtis, and others have found that they were able to cultivate torulæ from sarcomata in man, which, on injection into animals, were pathogenetic, and produced swellings in many respects similar to the sarcomata. Whether these swellings were really sarcomata it is impossible to say, but it seems more probable that they consisted of granulation tissue and were therefore inflammatory. Busse has described a torula which has pathogenetic properties and causes inflammatory foci, but the Italian authors deny that Busse and they are referring to the same micro-organism.

The parasitic theory of the new-growths is really an extension of the theory which ascribes tumour-formation to the action of an irritant, for, as we have already seen, no line can be drawn between the effects of an organised and a physical irritant. Nor can we draw a hard and fast line between inflammation and its sequels on the one hand, and tumour-formation on the other, especially as a chronic ulcer or scar-tissue may subsequently become the seat of a true tumour. Hence there is no inherent improbability that the new-growths, or rather the *malignant* new-growths, which form metastases should depend upon an organised irritant. Shattock and Ballance go further: thus they say, "in the matter of malignant growths more particularly it (*i.e.*, the parasitic theory) has much to recommend it,"[1] and, "the parasitic theory of malignant new-growths is so well grounded that during the past few years the whole of the work on the subject has been directed by it."[2]

But let us examine the grounds of the parasitic theory a little more closely.

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they show differential staining reactions. For a discussion of their possible relation to carcinoma the reader is referred to Klein's *Micro organisms and Disease.*

[1] *Loc. cit.*, p. 206.

[2] *Loc. cit.*, p. 210.

In the first place, it is very doubtful whether the microscopic appearances in cancer, to say nothing of sarcoma, indicate the presence of a parasite at all. Indistinguishable appearances can be found in many situations where there is no question of cancer, and in the rabbit's liver, where psorospermosis is exceedingly common, the changes to which presence of the parasite gives rise are different from cancer. Unless we grant the justice of considering the microscopic appearances as belonging to those of "cancer parasites," evidence in favour of the infective or parasitic nature of malignant new-growths is confined to the assumed similarity between carcinoma and sarcoma on the one hand, and infective diseases on the other, in the matter of metastases, and to the occurrence of cancer under such conditions as seem to indicate that the disease clings to certain houses.

In the second place, the similarity between malignant growths and such a disease as tuberculosis with regard to generalisation of the disease is superficial and not real. It only amounts to evidence that, in both instances, living cells may be carried from a local focus elsewhere by way of the lymphatics or the blood. In particular, it is no argument in favour of a parasitic cause for the new-growths.

Generalisation of a disease is not *of itself* an argument for the infective nature of that disease. When a solution of methylene blue is introduced into the subcutaneous tissue it is carried over the whole body by lymphatics and by blood-vessels, for it shows itself in the lymph of the thoracic duct and in the urine; but this form of generalisation does not imply that the methylene blue is an infective agent. Nor does the fact that when we find generalised tuberculosis or carcinomatosis or sarcomatosis the nodules are localised, make a difference, for it only shows that passage of the disseminated substance is obstructed at certain points. The important fact shown by the metastases in the contrasted cases of tubercle, cancer, sarcoma is therefore not that generalisation occurs, but that the disseminated substance (emboli) in each case contains cells which are living and capable of independent growth.

But the metastatic nodules themselves are totally different in the two contrasted conditions. This is better seen if we consider, not tubercle bacilli, but any of the pyogenetic cocci when they have become generalised and lead to the formation of pyæmic abscesses. The minute embolus of cocci carried by the lymph or blood-stream to a distant part, and so small that it may pass through all vessels but the capillaries, leads to the formation of a pyæmic abscess when it becomes lodged at some point, because the cocci are living, capable of multiplication, and capable of producing changes in the surrounding tissues. But the metastatic abscess formed in this way is not comparable with a metastatic nodule of cancer or sarcoma, because the secondary nodule of new-growth is not, like the abscess, the result of changes in the surrounding tissues produced by a living and multiplying factor, *but is the living and multiplying factor itself.* The nodule of new-growth may and does lead to changes in the surrounding tissues, and unless these are included in the conception of a cancerous or sarcomatous metastasis, a comparison between infective diseases and malignant new-growths on this point is not justifiable. Now, if we fill up this lacuna in the general acceptation of the term "metastasis" as applied to the new-growths, support for the parasitic theory derived from the occurrence of metastases falls to the ground. For then the tubercular or the pyogenetic microbes bear the same relation to the tubercular nodule or the pyæmic abscess as the whole cancerous or sarcomatous metastatic growth bears to the ignored changes in the surrounding tissues. Hence it is no more just, from the mistaken analogy of metastases, to argue that the multiplication of epithelial cells in cancer or of connective tissue cells in sarcoma is induced by the action of a micro-organism, than it would be just to argue that the multiplication of the tubercular or pyogenetic micro-organism is due to the action of another variety of micro-organism. In each case we have proliferation of cells, whether cancerous or sarcomatous on the one hand, or bacterial on the other, but neither case can help us to understand the essential cause of multiplication in the other.

In the third place, there is the evidence as to endemic location of malignant new-growths, especially cancer. Well-marked examples of this evidence are cited by Shattock and Ballance. In one example, within twenty-six years, six persons died of cancer in two houses that were under one roof and had a common drainage and water-supply; in the main the inhabitants of these houses were unrelated to one another. But an endemic distribution of cancer can be seen on broader lines. Thus, in England and Wales, Havilland has come to the conclusion that "the cancer-fields . . . . are found in the sheltered and low-lying vales traversed by fully formed and seasonally flooded rivers, and composed of the more recent argillaceous formations; and that the districts having the lowest death-rates from this cause occupy the more elevated areas composed of the oldest rocks, amongst which the *limestone* areas are coincident with the very *lowest* mortality." When we compare this distribution with the regions in which malaria is endemic, the general similarity, especially as regards moisture and absence of natural drainage, is striking. In the case of malaria it is known that an animal parasite is the cause of the disease, and this suggests that the same may be true in the case of cancer. Moreover, it is in favour of the suggested "cancer parasite" that it is animal and not vegetable, for the malarial parasites have not been grown on artificial media,[1] and attempts to cultivate the cancer parasite have been fruitless; so also malaria is not an infective disease in the sense that it may be transmitted from individual to individual, and the infectivity of cancer, if it exists at all, is of a very low order. This evidence is certainly of value; but on the whole, though we cannot deny the possibility that cancer (and sarcoma) may be diseases of parasitic origin, evidence in favour of that view is extremely small.

(5) *Theory of Anaplasia.*—Hansemann's theory of anaplasia is based on the assumption that the cells of a normal tissue, as they become more differentiated, progressively lose their capacity for growth, but regain it, and thereby lead to the formation of a tumour, if in course of time the cells revert towards an indifferent stage. His theory is an attempt to explain the supposi-

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[1] This is true of all the hæmatozoa up to the present time (February 1898).

tion that such a new-growth as cancer depends upon an increased capacity for growth on the part of the epithelial cells which enter into the composition of the tumour. Hansemann first of all held that the normality of a cell depends upon a particular kind of division of its nucleus. He found in carcinoma the so-called asymmetrical mitoses, and imagined that the smaller portion of the nucleus and the larger portion formed cells of different kinds, of which the larger approached to the indifferent stage. Strœbe, however, showed that asymmetrical mitoses are met in other rapidly growing tissues besides the tumours, so that Hansemann was obliged to relinquish this view. He still maintains, however, that the cells of tumours never show exactly the same histological and biological properties as the cells from which they sprang, and considers that this indicates that they have undergone a more or less widespread anaplasia.

(6) *Theory of Growth-Liberation.*—By this term I have ventured to designate Ribbert's theory to explain the new-growths. His theory of hypertrophy has already been considered (p. 540), and it has been shown that this author believes that in every cell there is a capacity for growth which is held in restraint by the "tissue-tension." When the tissue-tension is diminished the capacity for growth is set free, and proliferation of cells takes place. Carcinoma, for example, does not occur because the epithelial cells grow into a fibrous tissue, the resisting power of which is diminished, nor because the capacity for growth of the epithelial cells is increased, though each of these views has claimed, and still claims, many adherents. It occurs, according to Ribbert, because the tissue-tension is altered and the capacity for growth of the sub-epithelial fibrous tissue is set free, whereby it grows and invades the epithelium, breaking this tissue up, separating it into cells and groups of cells which (themselves being freed from tissue-tension) proliferate owing to the liberation of their own inherent, but hitherto restrained, capacity for growth. Ribbert's view concerning the formation of cancer, and, indeed, of many other kinds of growth, *e.g.*, fibro-adenoma of the breast, differs from that of other authors in that he makes the connective tissue portion of the growth play a

fundamental, and not as most other authors believe, a more or less passive, part. He argues against the theory which asserts that in carcinoma there is a direct in-growth of epithelial structures into the subjacent tissue, for he maintains that this has never been shown to occur beyond the possibility of doubt, and that the contrary is shown by some extremely early, but undoubtedly commencing, carcinomata which he had the opportunity of examining. This view, since it does not concern itself primarily with the manner in which the capacity of growth is liberated in a cell or group of cells, does not exclude of necessity either the traumatic theory or Cohnheim's theory of embryonic remnants. Indeed, in the case of some tumours, *e.g.*, cartilaginous tumours, rhabdomyoma, glioma, dermoid tumours, and some other kinds of cyst, all of which arise, or the germs of which are separated off, in intra-uterine life, Ribbert expressly invokes Cohnheim's hypothesis. In the case of chronic irritation, trauma, parasites, however, Ribbert holds that their importance in the ætiology of cancer consists in the fact that they lead to that proliferation of connective tissue which is a preliminary to the formation of a cancer, though it does not necessarily end in cancer-formation. Ribbert's theory has met with criticism, particularly at the hands of Ziegler, Hansemann, Hauser, and Notthafft, all of whom maintain that carcinoma commences with a proliferation of epithelium. To them Ribbert makes practically but one answer, viz., that they have not examined carcinomata in a sufficiently early stage, and that the periphery of an already established growth does not afford evidence upon the point.

Ribbert's theory offers certain manifest advantages. It presents one explanation for the whole group of tumours, whether they are simple or complex in structure, whether they are non-malignant or malignant, whether they correspond to embryonic or to adult tissue. It approximates tumour-formation to hyperplasia and regeneration, processes in which growth is also excessive. But it has the great disadvantage that it cannot readily be put to the test, owing to the rarity with which tumours are found in a sufficiently early stage, to be of use in deciding its value. On the whole, however, it is more satisfactory than any theory which has hitherto been put forward, as a working hypothesis.

With regard to the question, whether the fibrous tissue stroma of a growth plays a fundamental part in its formation, as Ribbert believes, there is some difficulty. In the case of papillomata, the view must be correct, for the fibrous tissue forming the basis on which the epithelium is placed in excessive amount, has obviously extended beyond the normal limits of the cutis vera. But when we bear in mind that any irritant of low intensity becomes surrounded by a capsule of newly-formed fibrous tissue, it becomes doubtful whether, in some cases, the fibrous tissue stroma of the growth may not be of the inflammatory type. The capsule that surrounds a *Trichina spiralis* in muscle, or a hydatid cyst in the liver, is fibrous, and is formed by the surrounding tissues as the sequel to a chronic inflammation, in the same way as the capsule is formed when one surrounds a bullet. The capsule which surrounds a fibro-adenoma of the breast is of the same nature, but the fibrous tissue in the growth itself is probably different, and is as much a part of the tumour as are the epithelial cells which line the clefts or cysts in the tumour. But, in the case of carcinoma, it is questionable whether we are to regard the fibrous tissue as a fundamental part of the tumour—therein agreeing with Ribbert—or whether we are to regard it as corresponding in nature to the fibrous tissue which forms a capsule around a non-malignant growth. Here, I think, the structure of a scirrhus of the breast helps us to a conclusion. If we examine the periphery of the tumour where it is actively growing, we see that it consists almost entirely of masses of epithelial cells, fibrous tissue being present in extremely small quantities. But in advance of the masses of epithelial cells there is always to be found a small-celled infiltration, a sign, that is, that the normal tissue is reacting to either an irritant or a stimulus. These small cells being invariably found in connective tissue, the most reasonable explanation is that they are proliferated connective tissue cells.

Now if we could imagine that proliferation of epithelial cells throughout the tumour ceased at a given moment, the proliferated connective tissue cells would form a capsule for the growth. But since this cessation in epithelial multiplication does not take place, but on the contrary new masses of epithelial cells are perpetually encroaching upon the zone of potential fibrous tissue in all directions, the surrounding tissues are in a constant state of striving to encapsule the growth, but never succeed in doing so. Nevertheless, the proliferated connective tissue cells form new connective tissue; and this connective tissue from the nature of the case does not enclose the cancer, but is enclosed within it. Here it becomes denser and contracts according to the normal properties of connective tissue, and hence the oldest parts of the growth are the densest and contain the fewest epithelial cells. The marked difference between the centre and the periphery of a scirrhus, as compared with the similarity between the centre and the periphery of such a growth as a fibro-adenoma of the breast, seems to me to imply a fundamental difference between the modes of fibrous tissue-formation in the two cases. I would therefore agree with Ribbert that in a fibro-adenoma of the breast the fibrous tissue of the tumour is a fundamental and essential part of the new-growth; but I should hesitate to agree with him that the fibrous tissue in a carcinoma (and especially in a scirrhus of the breast) is a fundamental and essential part of the new-growth in the same sense.

(vi.) **Cysts.**—The term "cyst" is used to imply an abnormal space containing liquid or semi-solid contents, and shut off from the tissues in which it lies by a wall which consists at least of fibrous tissue, though it is frequently more complicated. Besides the true cysts, for which this description suffices, hæmatoma is often included among the cysts, but it and allied conditions are better described as "false cysts."

The chief forms of cyst are as follow:—(1) Those containing an animal parasite, *e.g.*, a hydatid; here we have to distinguish between the true wall of the parasitic cyst from the fibrous tissue wall formed around it by the neighbouring tissues. (2) Cysts formed by enlargement of pre-existing ducts or cavities, the outlet of which has become obstructed: retention-cysts. These are almost invariably lined by a layer of epithelium, and they form the majority of cysts. Ranula, sebaceous cysts, hydrocele, cysts in fibro-adenomata, cysts in chronic granular kidneys, are of this nature. (3) Cysts formed by dilatation of a fœtal tube which is normally obliterated, *e.g.*, parovarian cysts. (4) Dermoid cysts. (5) Cysts formed by degeneration and liquefaction of the central portion of a solid mass, *e.g.*, cysts in many sarcomata. (6) Hæmatoma.

Concerning many of these, it is unnecessary to speak at length. Hæmatomata depend upon effusion of blood from ruptured blood-vessels, upon absence of coagulation in the effused blood, and upon the slowness with which absorption of a highly albuminous fluid takes place. Degeneration cysts may depend upon supervention of either the mucoid or the colloid change; the latter accounts for many of the cysts in goître. Degeneration may also be complicated by hæmorrhage, and then a condition is produced which may resemble hæmatoma; the contents of many kinds of cysts are coloured by altered blood-pigment.

In dermoid cysts, epithelium is the system of tissue most commonly represented; a dermoid cyst is not only lined by a well-marked squamous epithelium, but it also shows papillæ, sweat glands, sebaceous follicles and hair sacs (which are functionally active as shown by the greasy material and hair found in dermoid cysts). When the ovary is the seat of a dermoid cyst, not infrequently atypical teeth are planted on the epithelium, and sometimes these teeth may be set in a piece of bone somewhat resembling the alveolar bone of a jaw. The pathology of these two kinds of dermoid cyst is probably different. The ovarian dermoid (dentigerous) cyst is probably the remnant of a blighted ovum, but the cutaneous dermoid cyst, which is most commonly seen in the lines of the face and neck corresponding to the branchial clefts in the fœtus, is due to inclusion of a portion of the epiblast during closure of these clefts.

It is generally considered that retention-cysts are passive formations, *i.e.*, that secretion goes on behind an obstruction, and the accumulated secretion passively distends the duct on the proximal side of the obstruction. Their pathology is therefore similar to that of a dilated and distended urinary bladder in cases of impassable stricture of the urethra. It is necessary, under these conditions, that the secretion should be able to take place against considerable pressure, and therefore one would not expect to find cystic dilatation of the bile ducts a common condition; as a matter of fact, cysts in the bile ducts are almost, if not quite, unknown, though in some forms of jaundice the bile canaliculi throughout the liver may be wider than normal.

Ribbert, however, cannot accept the view that the retention-cysts are formed in the way described. He points out that in ranula the lining epithelium is often ciliated and the cells are markedly columnar, that in the congenital cystic kidney the epithelium is well formed though not always cubical, that in ovarian cysts, papillæ covered by a well-marked epithelium often project into the cavity of the cyst, and he points to these facts as showing that the fluid in the cyst is not under pressure. For if the fluid were under pressure the epithelial cells would be flattened. He applies his theory of growth-liberation to the cysts also, and assumes that the inherent capacity for growth of the connective tissue forming the wall of the obstructed duct is first set free; this alteration of tissue-tension sets free the inherent capacity for growth of the epithelial cells, which now proliferate and form new but normal epithelial cells. The clefts and spaces in a fibro-cysto-adenoma of the breast, he maintains, are formed in the same way. Hence this view implies that fluid is formed to fill a cyst, and not, as is usually believed, a cyst is formed to accommodate fluid that has already collected.

Ribbert's observations concerning the characters of the epithelium lining cysts are certainly correct, and it is important to remember that those regions, such as blood-vessels, lymphatics, urinary- and gall-bladder, which normally contain fluids under greater or less degrees of pressure are lined by a flattened epithelium. But it is impossible for anyone who has thrust a trocar into a hydrocele or an ovarian tumour, or who, in the post-mortem room, has opened a cyst in a granular kidney, to believe that the fluid contained in these cysts is not under pressure, and in some instances under considerable pressure. In the case of papilliferous ovarian cysts and cystic fibro-adenomata the matter is more difficult. For here we undoubtedly have growth of epithelium, and though in cystic fibro-adenoma the cysts are often more nearly represented by clefts than by definite cysts,—an appearance suggesting that they are subject to external pressure,—these clefts are seen to a greater or less extent even in the densest fibro-adenoma, and, in spite of this fact, the epithelium does not appear as if it had grown under pressure. In particular, there is none of that atrophy which we are accustomed to associate with pressure upon cells. Nevertheless, we do not know the relations of pressure to cell multiplication, and we do know that in an abscess, for example, living and apparently normal cells may be found though under considerable pressure, so that it is well, at present, to maintain an open mind upon the question.

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# CHAPTER XIII.

## The Pathology of various Morbid Conditions which are characterised by Abnormalities of Secretions and Excretions.

*Synopsis.*

I. General Considerations.

II. The Secretion or Excretion is excessive.
  (i) Diarrhœa.
  (ii) Polyuria.
  (iii) Hyperhidrosis.
  (iv) Ptyalism.
  (v) Galactorrhœa and Seborrhœa.
  (vi) Mucus.

III. Substances normally retained are discharged from the Body.
  (i) Blood.
  (ii) Albumin.
  (iii) Fat.
  (iv) Sugar.

IV. Substances normally discharged are retained within the Body.
  (i) Fæces.
  (ii) Urine and Urinary Constituents.
  (iii) Calculi.

V. Substances are discharged by Abnormal Paths.
  (i) Jaundice.
  (ii) Fistulæ and other Conditions.

VI. Secretions or Excretions contain Substances not normally present in the Body.

VII. Morbid Conditions of known or suspected dependence upon alterations in Internal Secretions.
  (i) Thyroid.
  (ii) Supra-renal Bodies.
  (iii) Pituitary Body.
  (iv) Sex-Glands.

The mere title that has been given to this chapter is an indication that under it will be considered a great variety of morbid conditions, many of which have no clinical relationship with one another. The only alternative method to the one adopted is to describe each secretion or excretion by itself. This method, though easier, is unsatisfactory, for two important reasons. Firstly, because the interest of a secretion or excretion from the point of view of pathology lies not in the secretion or excretion itself, but in the conditions of the body which cause abnormalities of that secretion or excretion; and secondly, because the inter-dependence of the secretions and excretions is so great that no one of them can altogether be considered apart from the others. Here, therefore, after giving a short description of the general processes upon which changes in the secretions and excretions may depend, we shall divide the morbid conditions themselves into the following classes:—

Morbid conditions in which the secretion or excretion is discharged in abnormally large quantities.

Morbid conditions in which substances normally retained are discharged from the body.

Morbid conditions in which substances normally discharged are retained within the body.

Morbid conditions in which substances are discharged from the body by abnormal paths.

Morbid conditions in which the secretions or excretions contain substances not normally present in the body.

Morbid conditions of known or suspected dependence upon alterations in internal secretions.

A perfect pathology would indicate the cause of each morbid condition, the tissues upon which that cause acts, and the processes whereby interference with function is brought about. At present we have but scanty knowledge upon many of these points; we know that certain end-results are produced, but of the processes leading up to them we are in many cases completely ignorant. Hence we are less liable to error if we work backwards from the end-results than we should be if we attempted to work forwards to them.

I. **General Considerations.**—The distinction that is generally made between a secretion and an excretion is that whereas a secretion is a product of glandular activity destined to be of further use in the body, an excretion is a useless product of glandular activity and is destined to be removed from the body. A more scientific method of separating the two processes is that advocated by Rose Bradford, and consists in regarding as excretions those products which are pre-existent in the blood, and are simply separated from it by the gland without undergoing any modification in the glandular protoplasm; and as secretions those products which are indeed separated from the blood, but which, in addition, undergo some elaboration in the gland-cells. Thus the water of pancreatic secretion upon this view is an excretory product, the trypsin (and probably also the saline constituents in some degree) are secretory products. Hence the same gland may have both secretory and excretory functions. Nevertheless, the old distinction is in many respects a useful one, and will often be employed in the following pages, but the meaning will be rendered clear by the context.

Those glands which are provided with ducts yield a secretion which can be recognised, and for this reason they are often said to afford an "external secretion." Glandular bodies, such as the thyroid, the supra-renals, the pituitary body, have no ducts, and since it has been found that from them substances can be obtained which have marked, and in many cases characteristic, effects, it is usually considered that these bodies elaborate materials derived from the blood, and return the altered substances directly into the blood without the aid of a duct; they produce no "external secretion," but they produce an "internal secretion." Some glands possess both kinds of secretion. In the case of the liver, bile is the external secretion, glycogen the internal secretion. In the case of the pancreas, too, there is much reason for believing that besides an external it has also an internal secretion. In other glands, such as the kidney, testis, and ovary, the existence of an internal secretion is not proved, though it is quite possible that one exists.

Whether in the fully formed state or as raw material, the constituents of every excretion or secretion of a gland have at one time or other circulated in the blood. To this statement there is no exception. But along with the true product of glandular activity we may have other substances of extraneous origin which may be looked upon as contaminations. Many of these contaminations can hardly be considered of hæmal origin at all. Thus, normal urine contains epithelial scales from the bladder and other parts of the urogenitary tract, normal saliva contains *débris* of epithelium and of food, normal sweat contains epithelial scales, and so on. In addition, the products of glandular activity are often contaminated by bacteria, and in practically all of them a certain amount of mucus is present. These contaminations may become highly important in pathological conditions, though they are unimportant from a physiological point of view.

The blood-pressure plays a great part in the formation of all glandular secretions, but in this matter the mean arterial blood-pressure (in the carotid, for example) is not so important as the blood-pressure in the artery supplying the secreting gland. Thus, in the kidney, though some cases of pathological polyuria occur under conditions in which we have reason to believe that the mean aortic blood-pressure is increased, and though there is no doubt that Ludwig and his pupils showed the great dependence of renal secretion upon aortic blood-pressure, yet even in pathological conditions a high aortic blood-pressure does not always co-exist with polyuria, and in physiology it can be experimentally shown that the two conditions often go in opposite directions. The high arterial pressure which follows upon stimulation of the spinal cord, or is seen in asphyxia and in poisoning by strychnine or digitalis, is not accompanied by an increased but by a diminished flow of urine, the reason of which lies in the fact that under all these conditions the renal arteries share in the general vasoconstriction throughout the body. But if, when the blood-pressure is high from one or other of these causes, the renal nerves are divided, spasm of the renal arteries gives place to dilatation, and the high pressure elsewhere shows its effects in the kidney by an increased flow of urine. Hence, in the case of the kidney, high aortic blood-pressure can only be associated with an increased formation of urine when the renal blood-vessels are at the same time widely dilated.

The dilatation of the renal arteries has two chief results with regard to the blood-flow through the kidney: it raises the capillary blood-pressure, and it increases the rate of blood-flow through the organ. According to the greater importance attached to one or other of these results, views differ as to the essential cause of the increased flow of urine, some authorities considering the increased flow as evidence of increased filtration through the glomerular epithelium, others considering it as dependent upon an increased vital activity of the kidney substance itself. Between these two views it is at present impossible to decide with certainty, but in the opinion of many authors, with whom I agree, the balance of evidence is against a purely physical explanation even for the separation of the water in urine. With regard to the constituents of urine other than water, evidence against a physical mode of excretion—within the range of ascertained physical processes—is very strong.

But the mean blood-pressure is not of equal importance in the case of all glands; thus, it has a more directly obvious effect upon renal secretion than it has upon the secretion of such a gland as the submaxillary. In the kidney the secretion of urine rises and falls with a rise and fall of renal blood-pressure, but in the submaxillary gland a secretion of saliva may be obtained by stimulating the chorda tympani after the head of the animal has been cut off and when the blood-pressure must therefore have fallen to zero, and may be absent though the blood-vessels are widely dilated, as when stimulation of the chorda tympani is carried out in an animal under the influence of atropin.

This brings us to a consideration of the effects of nerve-action upon secretion. In this respect there is a very great difference between different glands. The salivary and the sweat glands are well provided with nerves, both of cerebral and of sympathetic origin, and in the case of the salivary glands at least these nerves are associated with different functions, the cerebral nerves (chorda tympani and nerve of Jacobson) being associated with the separation of water and with vaso-dilatation, the sympathetic nerve being associated with the formation of the solids of the secretion and with vaso-constriction. The sweat glands are also provided with special nerves. These leave the spinal cord by the anterior roots in the dorsal and upper lumbar regions, and then enter the sympathetic system. In the case of the head and neck the hidrotic fibres run with the sympathetic, but in the limbs they run with the spinal nerves, having joined them after leaving the sympathetic. In all cases hidrotic nerves are closely bound up with vaso-motor nerves, but are distinct from them. In the case of some other glands the existence of definite secretory nerves is doubtful. Thus, Pawlow has determined that secretion of gastric juice is in some way bound up with continuity of the vagus nerve, and in the kidney it has been shown by Berkely that around the tubules and glomeruli there is a dense network of nerves. Bile, pancreatic juice, the secretion of the sebaceous glands, including the mamma, are all, so far as is known at present, formed without the intervention of other nerves than those which control the vascular conditions of the glands in question.

And yet the formation of secretions generally is influenced by the central nervous system. The salivation which accompanies thought of food, the arrest of salivary flow which is associated with fear, the sweating and the increased flow of urine which accompany mental emotions of different kinds, the arrest of milk secretion that may follow upon a sudden fright, are all evidence that secretory processes are controlled by cerebral processes. In some cases the glandular activity or quiescence is manifestly the result of a reflex nervous process; thus, the salivary flow that follows when dilute acetic acid is placed upon the tongue is a reflex act, in which the lingual and glosso-pharyngeal nerves convey afferent impulses. In other cases the process is not so certainly reflex; the fact that gastric secretion is poured out when food is masticated, but is prevented from reaching the stomach by ligature of the œsophagus, at first seems to suggest that gastric secretion is a reflex act. In part it may be so, but since soluble and digestible substances produce a far more copious flow of gastric juice than hard and indigestible substances, it is probable that secretion by the gastric glands depends—at least in part—upon their direct stimulation by substances absorbed from the food and carried to the stomach by the blood-stream. Pawlow believes that secretion of gastric juice is always a reflex act, but is largely called forth by psychic processes.

The selective influence which is exercised by the different glands upon substances presented to them in the blood is so well known that it needs no repetition here. In disease this selective influence is still present in most cases, but the inter-dependence of glands often comes into view in a way which it does not under normal circumstances. Thus, when the kidney is unable to remove urea, that substance may be removed by the gastric and sweat glands; when the kidney is unable to remove a sufficient quantity of water, it may be removed by gastric glands and lead to vomiting, or by intestinal glands and lead to diarrhœa. Drugs, too, have a selective influence upon different glands; thus the whole class of diuretic substances acts essentially upon the kidney, pilocarpine and atropin act markedly upon sweat glands, mercury and atropin upon salivary glands, while the action of belladonna (atropin) in bringing about arrest of milk-secretion is so pronounced as almost to be specific.

This short sketch of secretion and excretion generally must suffice. It is sufficient to show that in considering the pathology of morbid conditions accompanied by abnormalities in secretions or excretions we shall find in some cases that the fault lies in the gland itself, whether its protoplasm or its duct, in some cases that the fault lies in the blood with all the conditions which that implies, in some cases that it lies in the nervous system.

**II. Morbid Conditions in which the Secretion or Excretion is discharged in abnormally large Quantities.**— The quantities in which a secretion is normally poured out probably varies within very wide limits; but what these limits are we have very little knowledge except in the case of those materials which are discharged from the body in the form of urine and fæces. We know, however, that in "diabetes insipidus" the quantity of urine passed in the day may in some cases be ten times as great as normal; that in diarrhœa the material leaving the body by the bowel is increased; that in galactorrhœa there is an excessive flow of milk; in ptyalism an excessive flow of saliva; in hyperhidrosis an excessive flow of sweat; in seborrhœa an excessive formation of sebum. And in all these conditions the secretion or excretion is discharged in quantities that it is utterly impossible to regard as within normal limits. Moreover, the pathological nature of these states is in most instances, if not in all, indicated by the fact that the secretion or excretion itself differs from the normal.

Almost invariably the excessive discharge depends upon the presence of an excessive proportion of water. This is notably the case in diabetes insipidus, where the urine, instead of having a specific gravity of 1020 or thereabouts, may perhaps have a specific gravity of 1002; and in diarrhœa the substitution of a watery discharge in place of the normal semi-solid fæces also gives evidence of an abnormally large discharge of water. The same is true in ptyalism and in hyperhidrosis, for the saliva and sweat being little more than water, an excessive discharge of either means a corresponding increase in loss of water; in galactorrhœa, also, the milk becomes thin and opalescent. In seborrhœa the secretion is also modified, but it is probable that here the increase does not depend upon an increased discharge of water, since the sebum maintains its normal fatty nature, though it becomes thinner and more of the consistency of oil.

(i.) **Diarrhœa.**—Diarrhœa is a symptom of many diseases both grave and trifling. When we consider that normally the intestinal contents are fluid through nearly the whole length of the small and large intestine; that digestive fluids are poured into the bowel probably in large quantities over a great portion of its length; that absorption of fluid takes place over the whole length of the bowel, and particularly in the lower portion of the large intestine; that during their sojourn in the bowel the intestinal contents are subjected to constant muscular movements, the general tendency of which is to drive them towards the anus; and that the muscular and glandular processes are subject to the nervous system, it is clear that diarrhœa may depend (1) upon excessive output of fluid into the bowel, (2) upon insufficient absorption of fluid from the bowel, (3) upon excessive peristalsis, or (4) upon defects in nervous control. And this, without taking into account the fact that the whole digestive mechanism, considered in the widest sense, is liable to diseases of various kinds.

But the effects of disease may be summarily dismissed, for they act only through the medium of the four processes that have just been mentioned.

In most cases several of the four causes conjoin in the production of diarrhœa. Thus, when the condition follows upon ingestion of some irritating material, not only is peristalsis more vigorous, but on that very account a shorter time is allowed during which absorption can take place, and in addition, it is probable that the intestinal glands pour forth a greater amount of fluid (in particular, mucus) than normal in answer to the irritation. The diarrhœa which is associated with infective disease generally, but especially with cholera and typhoid fever, probably owns the same combination of causes. In all these cases there is, besides, reason to believe that absorption is actively diminished, apart from the shorter sojourn of the intestinal contents within the body; at any rate, there is clear evidence that absorption does not necessarily take place merely because a fluid is brought into contact with a tissue which normally absorbs such fluid.

On the other hand, in some cases one or other of the causes mentioned is so prominent that it overshadows the rest. Thus the purging which follows administration of such a drug as croton oil essentially depends upon an increased rate of peristalsis, that which follows administration of magnesium sulphate essentially depends upon a great increase in the amount of fluid poured into the bowel. Again, the "spurious" diarrhœa which accompanies the later stages of chronic obstruction of the lower portion of the large intestine is essentially due to failure of absorption; for in these cases the intestinal wall above the obstruction is covered by a thick coat of hard fæces—the accumulation of weeks or months—and the liquid intestinal contents from which alone absorption could take place are not brought into contact with the intestinal wall at all. So, too, the diarrhœa associated with various mental states is probably dependent upon increased peristalsis alone.

When, therefore, the pathological anatomy of any particular case accompanied by diarrhœa is known, it is generally easy to determine upon what cause or causes that diarrhœa essentially depends. Even then, however, the enquiry has only been shifted one stage further back in a large number of cases; it is easy to state the fact that "croton oil increases peristalsis," but it is at present impossible to say how it does so.

(ii.) **Polyuria.**—Under the name polyuria are included many different morbid conditions, in all of which, however, the flow of urine is increased. The most marked of these is "diabetes insipidus," in which, as has already been mentioned, the amount of urine passed in the twenty-four hours may be increased tenfold. Under the name diabetes insipidus we have to distinguish two conditions: (*a*) that in which there is an excessive flow of water, but in which the total excretion per diem of solid urinary constituents undergoes hardly any change; (*b*) that in which besides an excessive flow of water one or other of the solid constituents undergoes an alteration in amount of excretion, that alteration being generally in the direction of excess. One therefore distinguishes hydruria, azoturia (when there is excessive excretion of urea), anazoturia (when there is a deficient excretion of urea), phosphaturia (Tessier). More common than diabetes insipidus is diabetes mellitus, but the latter condition has characters so peculiar and important that it will be considered by itself and in connection with the sugar present in the urine. Nevertheless, it is probable that the excessive flow of urine in diabetes mellitus is of essentially the same kind as the excessive flow in phosphaturia or azoturia and perhaps also in hydruria. A fairly common condition in which polyuria occurs is hysteria; where hysterical patients do not manifest a marked deficiency in excretion of urine they often manifest a polyuria which is usually well-marked in connection with hysterical attacks. Most common of all morbid conditions, however, in which the secretion of urine is increased, is that associated with fibrosis of the kidney (chronic granular kidney). The polyuria is here not great, but it is definite and it may persist for years. Of all conditions leading to polyuria these five are by far the most important.

The pathology of polyuria generally is uncertain. We may perhaps associate the polyuria accompanying fibrosis of the kidney with increased blood-pressure. The left ventricle of persons whose kidneys are shrunken and fibrotic is almost always greatly hypertrophied, while at the same time the smaller arteries throughout the body are generally the seat of arteriosclerosis. As a result of these two conditions the blood-pressure in subjects of chronic granular kidney is high, and this may explain the polyuria. This at least is the view put forward by Cohnheim and held by many authorities at the present day. In the case of diabetes insipidus it is generally held that the increased flow of urine is due to a local diminution of pressure in the renal artery brought about by nervous causes through the medium of vaso-motor nerves. In favour of this view it is pointed out that injuries of the brain and tumours, especially those in the region of the fourth ventricle, are often found to be associated with the condition.

But it is a question whether all forms of polyuria must be referred to an increase in the amount of blood that passes through the glomeruli in unit time or to increased glomerular blood-pressure. In other words, it is a question whether variations in amount of urine may not be to some extent independent of the circulation. Ludwig long ago suggested that water is absorbed from the urine during its passage down the urinary tubules. This view, which derives some support *à priori* from the anatomical arrangement of blood-vessels and tubules in the kidney, has received experimental support at the hands of Ludwig, Hermann, Heidenhain, and others. Tuffier found that a solution of strychnine placed in the pelvis of the kidney is absorbed and the drug manifests its physiological action. Huber came to the conclusion that absorption takes place from the tubules and not from the pelvis of the kidney at all, but that absorption actually does take place he showed by filling the pelvis with a solution of potassium iodide under a pressure of about 38 mm. of water; he recognised the drug in a short time in the saliva of the animal. Hence there is some reason to believe that a transference of fluid can take place from the urinary tubules to the blood-vessels under normal conditions. Further —whether we regard it as evidence of osmosis or as evidence of secretion—there is no doubt that when a strong solution of a crystalloid is separated from the blood by a thin living membrane, it is in the highest degree common for fluid to pass from the blood through the membrane to the solution of crystalloid.

Now it is conceivable, even if the output of the glomerular blood-vessels remained constant, that polyuria might be produced either by a failure of absorption in the kidney or by an increased output of fluid from the blood-vessels into the urinary tubules.

In the cases of diabetes mellitus, of phosphaturia, and of azoturia the percentages of sugar, of phosphate, of urea in the urine are greater than they are in the blood, and so long as the urines in these diseases were separated from the blood by a thin membrane, as they were while passing along the urinary tubules, it is reasonable to suppose that fluid passed into them from the blood. But even if that were actually not the case, absorption of more highly concentrated solutions of crystalloids takes place from peritoneal or pleural cavity less rapidly than absorption of more dilute solutions. So that if it be allowed that there is an interchange of fluid between the urinary tubules and the capillaries that surround them, the existence of polyuria in diabetes mellitus, in phosphaturia, and in azoturia becomes intelligible; either it would depend upon an actual increment of fluid in the urinary tubules, and this seems the more probable, or it would depend upon a diminished absorption of fluid from these ducts.

In the case of chronic granular kidney also it seems more reasonable to associate the polyuria with diminished absorption than with increased secretion. Even if it be granted that the aortic blood-pressure in such cases is increased, the diminution in numbers of glomeruli, the thickness and rigidity of the renal blood-vessels, which are characteristic of the fibrotic kidney, argue rather for a diminished total output of urine through the glomeruli than for an increased total output. But examination of a microscopical section of such a kidney renders it in the highest degree probable—once the possibility of absorption from the urinary tubules is allowed—that in such a kidney absorption must be reduced to a very low point. The large amount of fibrous tissue which separates individual tubules, which is situated in a region where normally the amount of fibrous tissue is minimal, and which surrounds the inter-tubal blood-vessels as with a thick sheath, must present a great obstacle to the passage of fluid from the urinary tubules to the blood-vessels. If absorption takes place at all in the normal kidney the contracted granular kidney is essentially one in which absorption would be prevented.

In the case of simple hydruria (as in the case of hysterical polyuria) we have nothing to help us. The kidney shows practically no morbid changes, the urine shows the presence of no abnormal amount of crystalloid. There remains only the fact that the onset of hydruria is said not infrequently to follow upon various brain conditions which are often of an obscure kind. But even if this be the case we are no nearer to an elucidation of the pathology of hydruria, for it would be in the highest degree astonishing if these lesions were able to induce a relaxation confined to the renal blood-vessels alone. That they might cause paralysis of vaso-motors generally is conceivable, but in that case the mean blood-pressure would fall and the secretion of urine, though it might be somewhat increased, would certainly not be increased as it is in hydruria. For the production of hydruria by vaso-motor changes alone it is at least necessary that the cerebral lesion should single out the renal vaso-motor nerves for paralysis, a condition that would be so remarkable that one is justified in asking whether the cerebral conditions have any causal relationship with the hydruria at all. It must be confessed, however, that no better explanation can be put in its place; the idea that hydruria depends upon a diminished absorption of water in the kidney suggests itself, but is a pure surmise.

(iii.) **Hyperhidrosis.**—The secretion of an abnormally large amount of sweat may be more or less general, as in the critical sweating of fever, the night-sweats accompanying pulmonary tuberculosis, or the sweat of collapse; or it may be strictly localised as in the unilateral sweating of the face and neck that sometimes accompanies aneurysm pressing upon the sympathetic nerve. In some cases sweating is due to central causes, as for example when it is called forth by emotions; in other cases, to direct stimulation of hidrotic nerves, as when a tumour presses on the sympathetic. Frequently hyperhidrosis is reflex, being brought forth by pain, *e.g.*, the pain accompanying passage of a renal or a biliary calculus. But sometimes the sweating seems to approach more to the condition (known as "paralytic secretion" of saliva) which follows upon section of the chorda tympani. The hidrotic nerves being closely bound up with the vaso-motors, vascular changes, and in particular, dilatation of arteries, accompanies hyperhidrosis. But this is not always the case, for in the "cold sweats" of pulmonary tuberculosis the skin is often anæmic and cold.

(iv.) **Ptyalism.**—Ptyalism is chiefly associated with tumours of the medulla oblongata (bulbar paralysis) and with poisoning by mercury and by the bromides and iodides. In bulbar paralysis it is possible that the salivation may in part be spurious and dependent only upon a difficulty in retaining and in swallowing the saliva. But it is probable that there is in addition an actual excess of saliva secretion. Whether this would then depend upon irritation of a centre in the bulb, or upon a condition akin to that of paralytic secretion, it is impossible to say. Cohnheim gives his verdict in favour of the former explanation because of the length of time that a patient suffering from bulbar paralysis may exhibit ptyalism, and in this view he is followed by most modern writers, though not by all. The ptyalism following administration of iodides in large quantity seems to depend upon the fact that these salts are selectively excreted by the saliva. The ptyalism following administration of mercury is probably reflex and is induced by the stomatitis which is present in such cases.

(v.) **Galactorrhœa and Seborrhœa.**—The pathology of galactorrhœa and of seborrhœa is unknown, but perhaps they depend upon conditions similar to those which obtain in the later stages of "paralytic secretion" of saliva. When the chorda tympani has been cut there results a hyper-secretion of saliva which is of nervous origin and which, for one or two days after division of the chorda tympani, can be stopped by division of the sympathetic on the same side. But if division of the sympathetic be delayed for more than about two days, its section has no effect upon the flow of saliva at all; ptyalism goes on as before, but brings along with it an atrophy of the gland. In the case of the breast and sebaceous glands, definite secretory nerves are not known to exist, so that we cannot speak of a true "paralytic secretion." But just as local changes in a salivary gland severed from its nervous connections can lead to a hyper-secretion of saliva, so it is possible that local changes in breast or in sebaceous glands may lead to a hyper-secretion of milk or of sebum respectively. What those local changes are, however, it is impossible to say.

(vi.) **Mucus.**—Reference has already been made to mucus in connection with the mucoid change (p. 520). Mucus is produced in abnormally large quantities whenever a mucous membrane, whatever its situation, is subjected to the action of an irritant. Whether animal parasites irritate the rectum or acrid gases the bronchi, whether a polypus irritates the cervix uteri or gonococci the conjunctiva, the result is always an excessive formation of mucus. But the pathology of this hyper-secretion is uncertain. We know, in such a mucous gland as the submaxillary, that storage of granules occurs in the cells when the glands are "resting" or when the sympathetic is stimulated; we know also that some at least of these granules are mucigenous and become converted into mucin after they have been discharged from the cells. But whether we may apply this knowledge to the excessive formation of mucus that accompanies irritation of a mucous membrane is doubtful. For in the mucous membranes generally, one finds simple crypts or isolated goblet-cells rather than glands supplied with a perfect nervous supply such as that of the submaxillary gland. And though it is possible that excessive formation of mucus may depend upon an abnormally large secretion of mucigen, it is probable that the process approximates more closely to mucoid degeneration.

As it is not proposed to make a special class of morbid states in which the secretions and excretions are discharged in abnormally small quantities, but to consider conditions such as constipation, anuria, etc., under another heading, it will be well just to mention here that morbid states are known in which secretions are arrested or greatly diminished. Thus, in xerostomia, little or no saliva is secreted, with the result that the mouth is dry and the tongue becomes cracked; in xeroderma, secretion of sebum fails and the skin becomes hard, dry, and cracked. In diabetes mellitus, and in renal disease, secretion of sweat is diminished, as it is also during the height of fever. It has already been said that there is reason to believe that in fever all digestive secretions are diminished; in the case of saliva this is markedly the case. The pathology of many of these conditions is not clear, but in the case of sweat and saliva the fundamental cause is probably nervous.

**III. Morbid conditions in which Substances normally retained are discharged from the Body.**—This class of morbid condition becomes highly important from the fact that loss of material which is normally retained within the body leads to mal-nutrition and wasting. But though progressive emaciation especially characterises the diseases of this group it also occurs in some diseases of the last group. Thus, profuse and continued diarrhœa, galactorrhœa, and "diabetes insipidus" lead to great wasting, while the excessive sweating that occurs in many cases of pulmonary tuberculosis is an important cause of the great wasting characteristic of consumptive patients. From this point of view the last group is but a special sub-division of the present one.

The chief substances that call for notice in this section of the present chapter are (1) blood, (2) albumin, (3) fat, (4) sugar, and they will be considered in this order.

**(i.) The Substance discharged is BLOOD.**—The whole question of hæmorrhage having been considered in a previous chapter we shall leave entirely on one side conditions such as epistaxis, hæmoptysis, hæmatemesis, menorrhagia, metrorrhagia, hæmophilia, etc., in which the morbid condition is one of hæmorrhage differing only in detail from the hæmorrhage that results from severing an artery. Moreover, the blood lost in these morbid conditions is only accidentally found in a secretion or excretion—it is not an integral part thereof, as is the blood in the conditions immediately to be noticed. Passing over the rare cases in which blood is secreted with the sweat (hæmathidrosis), if indeed such a condition really exists, we have to consider the loss of blood in (*a*) the fæces and in (*b*) the urine.

(*a*) When blood is passed with the stools it may either present the normal appearance of blood, or a condition (melæna) may be produced in which the stools are of the appearance and consistency of tar. When the blood is of normal appearance it is certain that the seat of hæmorrhage is not far above the anus. Almost any morbid condition of the rectum may be accompanied by the passage of bright blood, but the commonest is hæmorrhoids. In melæna, on the other hand, the seat of hæmorrhage may be anywhere in the alimentary tract down probably to the sigmoid flexure. Thus the stools may be tarry if profuse bleeding from the nose have taken place and the blood have been swallowed, though a far commoner cause of melæna is the gastric hæmorrhage which arises in the course of either gastric ulcer or alcoholic cirrhosis of the liver. So, too, melæna occurs when the seat of hæmorrhage is a duodenal ulcer or a typhoid ulcer of the ileum. When bleeding takes place from the mucous membrane of the lower portion of the colon, the blood is not subjected to digestive processes either in the same degree, or for the same length of time, as it is when poured out high up in the alimentary canal, and the blood itself is therefore less altered. In ulcerative colitis, for example, though hæmorrhage is fairly constant, the stools are not tarry, though they may be dark; often they show the presence of solid masses of disintegrating blood-clot. The colour of the stools in melæna is due to the presence in them of sulphide of iron formed by combination of the sulphuretted hydrogen present in the lower bowel with the iron of the disintegrated hæmoglobin.

(*b*) In considering the morbid conditions in which blood is lost to the body in the urine, we may omit mention of those cases in which the blood comes from urethra, prostate, or bladder, for they are strictly comparable with cases in which blood is lost from the lower end of the bowel. Whether from the presence of a polypus, ulcer, or from any other cause, blood is poured out and is passed either in unaltered condition or as blood-clot in both cases. In passing, however, it may be mentioned that the chief parasitic cause of hæmaturia—the ova of *Bilharzia hæmatobia* [1]—is found in the blood-vessels of the vesical wall, and by causing their rupture leads in large measure to the hæmaturia that is characteristic of infection by this hæmatozoon. In the case of the rectum we have a parallel condition, for, according to Guillemard, passage of blood by the bowel may sometimes be one of the earliest signs of infection by Bilharzia.[2]

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[1] *Bilharzia hæmatobia* is a trematode platyhelminth or fluke, which inhabits the veins of man, monkeys, and probably also cattle and dogs. Though the flukes are for the most part hermaphrodite, in this species the sexes are distinct. The male is 7–16 mm. in length, and the lateral margins of the body are bent over ventrally to form a channel—the gynæcophoric canal—in which the female lies during copulation. The female is about 20 mm. in length, darker and finer than the male. The ovum, which is most important as it is the cause of symptoms in the disease, can usually be recognised with ease in the urine ; it is an oval body of which the length is about ·12 mm. and the breadth about ·06 mm. The egg case is transparent and through it the embryo can readily be seen. At one pole the ovum ends in a small but acutely pointed spine which is quite characteristic. The embryo within the ovum is as a rule nearly mature, and in pure water the ovum often hatches in two or three minutes. The young worm is covered with cilia over the whole body excepting the mouth, and darts to and fro with great rapidity. The life history of the animal is unknown as is also the mode of infection : in those countries in which endemic hæmaturia occurs (viz., Egypt, Cape Colony, Natal, Transvaal, and discontinuously over the whole of Africa), it is commonly held that the parasite gains entrance to the body during river-bathing, and there are reasons for believing that this view may be correct. In the human body Bilharzia may be found in various parts, but its focus appears to be the smaller branches of the portal vein. The ova are deposited in the finer communications between the portal and the systemic venous systems, and it is for this reason that bladder, rectum, kidneys, and ureters are the principal parts affected.

[2] *Anchylostomum duodenale*, which, so far as loss of blood is concerned, bears the same relation to the intestine as does Bilharzia to the urinary organs, "sometimes though rarely causes the stools to have a reddish-brown tinge from sanguineous admixture" (Manson).

The morbid conditions, therefore, with which we shall especially be concerned are (α) those in which red blood-corpuscles appear in the urine as the result of changes in the kidney, and (β) those in which hæmoglobin appears in the urine as the result of changes in the blood.

(α) *Hæmaturia of Renal Origin.*—When renal changes lead to the appearance of blood-corpuscles in the urine, the urine may present every gradation of colour from an apparently normal yellow to a condition in which the liquid is apparently pure blood. This, of course, depends upon the number of red blood-corpuscles present. But in a large number of cases the urine is not red at all, but has a peculiar "smoky" appearance, which is seen on microscopic examination to be due to the presence of discrete red blood-corpuscles. The corpuscles in urine do not preserve their normal biconcave shape, they may become spherical or crenate, and they lose the tendency to agglomerate in rouleaux. Hæmaturia dependent upon kidney changes is generally due to acute nephritis or to renal calculus or to malignant disease; occasionally, but very rarely, blood is found in the urine when the kidney is the seat of tubercular disease. Hæmaturia due to laceration of the kidney by violence does not call for special consideration.

The hæmaturia of acute nephritis is merely a special example of the law that in inflammation, when congestion is very acute, diapedesis of red blood-corpuscles is a prominent symptom. In accordance with this statement we find that hæmaturia is an early sign of acute nephritis; "a man gets drunk, sleeps in a ditch, and passes bloody urine the next morning." So also the escape of blood is most marked in those situations where blood-vessels are most numerous, viz., the glomeruli. A section of a kidney in the earliest stage of acute nephritis shows the glomerular blood-vessels engorged, often ruptured, and the glomerular space crammed with red blood-corpuscles; often, too, solid cylinders of corpuscles block the tubules for a greater or less portion of their length. If the patient survives, as the inflammation becomes more chronic the hæmaturia passes off, but it is many months before corpuscles are completely absent from the urine. Hæmaturia is common to nephritis of all kinds, so long as it is early and of some severity, but it is especially well marked in nephritis due to cold or to poisoning by cantharides or oil of turpentine. Changes in the kidney sufficiently severe to allow the passage of blood-corpuscles through the glomerular blood-vessels lead to other changes in the urine to which reference will be made later.

The hæmaturia accompanying renal calculus is essentially due to traumatism of the kidney substance or of the pelvis of the kidney, and the hæmaturia will be marked or slight according as the physical characters of the calculus render it more or less likely to produce lacerations; a smooth uric acid calculus produces less hæmaturia than a rough and tuberculated calculus composed of calcium oxalate. As might be expected, it is characteristic of this type of hæmaturia that it is aggravated by exercise or jolting. Calculous hæmaturia calls for no special remark. Unless there be complications, the urine itself, considered apart from the blood, approximates closely to the normal in characters and in quantity.

Hæmaturia accompanying malignant disease of the kidney may be due either to hæmorrhage from the kidney substance itself (congestion of the kidney being induced by the irritant action of the new-growth), or to hæmorrhage from the malignant growth. In the former case there is nothing peculiar with reference to the hæmaturia, but if there be disintegration of the malignant growth and hæmorrhage come from it, cells or even small portions of the neoplasm itself may be found in the urine.

(β) *Hæmoglobinuria.*—But blood is not always lost to the body in a corpuscular form. Morbid conditions are known in which the urine contains dissolved hæmoglobin.

The urine in hæmoglobinuria may present macroscopic characters identical with those of hæmaturia, it may be pink or blood-red, or the colour of porter; but it never presents a "smoky" appearance. Microscopic examination, however, suffices to distinguish hæmoglobinuria from hæmaturia at once, for in hæmoglobinuria, blood-discs are absent from the urine. Spectroscopic examination of the urine shows the presence of the well-known absorption bands of oxy-hæmoglobin (in the yellow and the green between the solar lines D and E), and in addition a broad band in the red between C and D but nearer C, the absorption band of methæmoglobin. On heating urine containing hæmoglobin a precipitate is thrown down, or in marked cases the urine may become solid; the precipitate consists of globulin coloured with blood-pigment.

Hæmoglobinuria occurs in all cases in which there is extensive destruction of red blood-corpuscles and solution of hæmoglobin in the blood-plasma. It occurs after transfusion with actual blood whether before or after defibrination, and especially if the blood have been derived from an animal differing in species from that into which it is transfused. According to Cohnheim, it occurs in animals after extensive superficial burns, but whether this is also true for human beings is doubtful. It has been recognised in man after poisoning with chlorate of potash, nitro-benzol, arseniuretted hydrogen, hydrochloric, sulphuric, and carbolic acids; in some of these cases the presence of hæmoglobin dissolved in the blood-plasma has been recognised during life. Winckel relates the history of an epidemic which killed twenty-three out of twenty-four new-born infants who were attacked in a lying-in institution in Dresden; no explanation could be given of this epidemic.

But the most important as well as the most interesting forms of hæmoglobinuria are those which, from certain of their characteristics, seem to have relationships with malaria.

According to Fayrer, hæmoglobinuria is apt to occur in some forms of malarial fever, and Crosse has shown that this occurs much more frequently in Africa and other tropical regions than in India. Besides its appearance as a symptom or complication of malaria, there occurs, especially in western Equatorial Africa, a disease which is known by the names of "hæmoglobinuric" or "blackwater" fever. Next, a condition is occasionally met with in temperate climates in which the patient, without otherwise suffering greatly, passes from time to time urine containing hæmoglobin. And lastly, in patients of the last category a mild attack may not lead to a paroxysm of hæmoglobinuria but to a paroxysm of albuminuria. Four closely allied conditions are therefore known: (1) malarial hæmoglobinuria, (2) hæmoglobinuric fever, (3) paroxysmal hæmoglobinuria, (4) paroxysmal albuminuria.

Now, so far as the blood condition is concerned, there is a great similarity between the first three of these conditions. It has already been said that destruction of red blood-corpuscles is characteristic of malarial fevers, and though the plasma does not usually contain dissolved hæmoglobin, it is not difficult to believe that such should sometimes be the case, especially when it is remembered that malaria accompanied by hæmoglobinuria is malaria of a severe type. In hæmoglobinuric fever there is no doubt that severe blood changes, and especially hæmolysis, occur; moreover, the corpuscles are paler than normal and the plasma is reddened. In paroxysmal hæmoglobinuria, Ehrlich found in a woman subject to the disease, when he bound an elastic bandage round one of her fingers and caused her to place it in water at 0° C. for a quarter of an hour, that the red blood-corpuscles were broken up and the blood-plasma took on a markedly pink colour; the changes do not occur under similar conditions in a normal person.

With regard to ætiology, also, certain points of resemblance may be noted. In the case of malaria the existence of an animal parasite as cause of the disease is undoubted, and there is no difficulty in understanding the pathology of malarial hæmoglobinuria. The pathology of hæmoglobinuric fever is not quite so clear; it occurs in regions where malaria is most severe, and in the blood of patients suffering from hæmoglobinuric fever the existence of animal parasites has been described, but they have not always been found with the constancy that might be expected if the disease is purely malarial, nor are the characters of such micro-organisms as have been described very definite. Though one must speak with some reserve, one is nevertheless probably correct in regarding hæmoglobinuric fever as dependent upon the presence in the blood of an animal—perhaps the malarial—parasite. In the cases of paroxysmal hæmoglobinuria and albuminuria, the relationship of these conditions to exposure to cold is undoubted. In a person subject to either of them, exposure to cold for a few minutes leads to hæmoglobinuria or albuminuria, which may last perhaps for an hour or two, perhaps for a whole day. The degree of cold to which the patient must be exposed in order to induce an attack is variable, but always very slight, as compared with that which can be borne by a healthy person without any discomfort whatever. Standing in a draught of air for a short time, thrusting the arms or feet into cold water will bring on an attack. The patient is in most cases conscious of no discomfort, but notices the next time he passes water that the urine is the colour of porter; with each successive micturition it becomes paler until, after the bladder has been emptied three or four times, the urine is again normal. Where the condition is albuminuric and not hæmoglobinuric, of course, the condition is only recognised by chemical examination.[1]

Now there are two connecting links between the severe forms, malarial hæmoglobinuria and hæmoglobinuric fever, and the slight forms, paroxysmal hæmoglobinuria and paroxysmal albuminuria. Firstly, paroxysmal hæmoglobinuria and albuminuria, like malaria, yield more readily to quinine than to any other drug. In this respect hæmoglobinuric fever is exceptional, for it is agreed by most of the competent authorities that not only is quinine useless, it is positively injurious. Secondly, exposure to cold is a predisposing cause to attack in the case of each disease. With regard to paroxysmal hæmoglobinuria and paroxysmal albuminuria, we have already spoken, but it is a matter of common knowledge that change of residence to a cooler climate is often at first accompanied by malarial attacks in a person who has lived in a malarial district, though when living in that district he may have been free from attacks. The same is true also of hæmoglobinuric fever.

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[1] Hæmoglobinuria is also sometimes seen in man as the result of muscular exertion. Thus Lee Dickinson reports three cases in which the condition occurred after athletic exercises, and adverts to other recorded cases. Apparently it is not necessary that the muscular exertion should be extraordinarily severe, occasionally, walking is sufficient. The hæmolysis has been ascribed to poisoning by accumulated carbonic acid. Besides a hæmoglobinuria, an albuminuria from exertion is also known, and it is important to note that sometimes the two conditions alternate in the same patient.

It is probable, therefore, that there is some connecting link between the four morbid conditions. But whether this concerns the ætiology of the disease, and suggests that hæmatozoa should be sought for in paroxysmal hæmoglobinuria and paroxsymal albuminuria, or whether it suggests that the same unduly labile condition of red blood-corpuscles exists in all four diseases, and can be produced by different causes in each, it is impossible to say. Bearing in mind the fact that toxic hæmoglobinuria is with certainty known to exist, the latter suggestion seems more probable, for in toxic hæmoglobinuria there is, of course, no question of a hæmatozoon. But if a labile condition of the red blood-corpuscles be the fundamental cause of hæmoglobinuria, it probably depends upon some chemical change induced by toxic substances, and here we are met by the difficulty that there is at present a complete lack of evidence that toxic substances are formed by hæmatozoa of any description.

(ii.) **The Substance discharged is ALBUMIN.**—It seems at first sight unreasonable to distinguish cases in which blood is discharged from the body along with the secretions or excretions from cases in which albumin is discharged, considering that blood is an albuminous fluid. But the distinction is advisable because of the clinical differences between the two groups of cases. To the physician and surgeon, hæmaturia and albuminuria, for example, are terms calling up different mental pictures, though with hæmaturia there is albumin in the urine, and with albuminuria there is generally present a smaller or larger number of red blood-corpuscles.

It is a remarkable fact that, with one great exception, none of the materials that leave the normal body contain albumin, or, at most, contain it in the merest traces; fæces, urine, sweat, tears, sebum, are normally free from albumin. It is only in connection with processes of reproduction that the normal body departs from the rule; menstrual blood, semen, the products of conception, milk are albuminous. To maintenance of the species alone is the benefit of the individual subordinated.

In disease, on the other hand, the body often suffers loss of albumin. It may be lost in fæces or in urine, in inflammatory exudations, in pus, in peritoneal and pleural effusions, in œdema fluid, and so forth. A less evident but even a more severe loss occurs where albumin is used for the nutrition of a tissue physiologically outside the body, such for example as a new-growth. But with most of these—important though they are—we are not immediately concerned, as the albumin is not lost with a secretion or excretion. We have here only to discuss loss of albumin by the bowel and by the kidney.

Before going further it is necessary to mention what is signified in this connection by the word "albumin." In the vast majority of cases serum-albumin and serum-globulin are the two varieties with which we shall be concerned, but in some cases albumoses, and in others nucleo-proteids, will claim attention. Discharge of undigested proteid food, whether by vomiting or by the bowel,[1] will not detain us.

(*a*) *Loss of Albumin by the Bowel.*—Loss of albumin in the fæces is apparently not a common condition; but though the subject has not received great attention, a few important conditions are known in which it occurs. *A priori*, one would not expect to meet many forms of disease accompanied by loss of albumin in the stools. For when one bears in mind that digestion and absorption of proteid is one of the chief functions of the intestine, and that the intestine normally contains myriads of bacteria which break up proteid, it is clear that we must not expect to find large amounts of albumin in the stools, unless (1) the morbid process involving the intestine is of extreme severity, or (2) the portion of intestine affected is not far removed from the anus. When we find in so severe a disease as Asiatic cholera, in which the mucous membrane of the entire intestinal tract is congested and swollen or even shows local excoriations or ulcers, that the evacuations contain not more than ·2–2 per cent. of albumin (Parkes), it is intelligible that in mild forms of diarrhœa, albumin should be absent. Hence in the large majority of cases presence of albumin in the stools may be taken as evidence of disease affecting the lower part of the large intestine. The most important disease in which albumin is discharged by the bowel is that which is known under the name of "dyspeptic membranous colitis" (Hale White) or "desquamative enteritis" (Light). In it complete tubular casts of the intestine are evacuated, usually one to six inches but sometimes several feet in length; the membrane is laminated and "chemically consists of albumin; it contains no fibrin" (Hale White). In other diseases of the large intestine it is not known that albumin (apart from that which is contained in blood) is discharged; mucus is certainly discharged in many of these diseases and in large quantities, but whether albumin is also discharged is at present uncertain.

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[1] The fact that, after extirpation of the pancreas in dogs (Abelmann) and in obstruction of the pancreatic duct in man (Vaughan Harley), absorption of proteid by the intestine is considerably reduced, and therefore undigested proteid given in the food appears in the stools, may just be mentioned.

(*b*) *Albuminuria.*—The term albuminuria is used to cover all conditions in which a substance yielding the ordinary proteid reactions and not blood is present in the urine. In albuminuria the proteid is essentially in solution, though in many of the more severe cases solid proteid is present in the form of "casts" of the urinary tubules. The proteid in albuminous urine is, in the great majority of cases, a mixture of serum-albumin and serum-globulin, the proportions of which to one another vary in different cases and according to circumstances with which we are at present ignorant. In other cases the proteid is an albumose,[1] and, according to von Friedländer, in yet others a nucleo-albumin. According to the differences between their proteid constituents the chemical properties of the urine vary; urines containing serum-albumin and serum-globulin throw down a coagulum on heating if the urine be slightly acid, those containing albumose do not throw down a coagulum on heating but do so on saturation with ammonium sulphate or on addition of large quantities of alcohol, and so on.

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[1] It was for some time held that the urine contains peptone in certain morbid conditions and the name "peptonuria" was coined, but with advance of knowledge as to the characteristics of the albumoses it was shown that the "peptone" is not true peptone but in reality "albumose." Hence the condition is now commonly known as "albumosuria." In the same way it will be necessary to separate from "albuminuria" a sub-class, "nucleo-albuminuria."

But with chemical differences of this description we are not concerned, they must be sought in works on physiological and pathological chemistry.

The first question that naturally arises in enquiring into the pathology of albuminuria is, Why is the normal urine free from albumin? If we could answer this question satisfactorily we should be far on the way towards a knowledge of the pathology of albuminuria, but unfortunately we can derive little help from physiology in this respect. Indeed it is more just to say that upon this point the processes of pathology have taught to physiology the little that she knows.

At first sight one might suspect that the answer is to be found in the slowness with which diffusion and filtration of albumin take place. And when Leube, Munn, Furbinger and others stated that one out of seven or eight healthy individuals passes albumin in the urine, and when Senator came to the conclusion that slight albuminuria is a physiological phenomenon, it was believed by many that the filtration hypothesis of Ludwig sufficiently explains the freedom or comparative freedom of the urine from albumin. But against all such beliefs there was advanced the incontrovertible fact discovered by Stokvis, that when dissolved egg-albumin is injected directly into a vein or beneath the skin, an albuminuria sets in which lasts until all the egg-albumin has been removed from the body. Differences in rates of diffusion and filtration between these two varieties of albumin are insufficient to explain this fact.

This step having been made, it was natural to turn from the "filtering" fluid and look towards the "filter" for an explanation. At the time when Ludwig was formulating his filtration hypothesis for urine-formation, the vital theory of Bowman claimed many adherents. This theory, which regarded the urine as a secretion and not as a filtrate, was supported and advanced by Heidenhain, Nussbaum, and others. It is unnecessary here to enter into details of experimental work that is fully discussed in treatises upon physiology, but as the result of this work it was shown conclusively that certain constituents of the blood, normal and abnormal, are removed by the epithelial cells of the convoluted tubules and the ascending limbs of the loops of Henle. Moreover, it was shown that though no sugar is removed by the kidney when it is present in the blood in quantities less than about 1 per mille.,[1] when it exceeds this amount the urine contains sugar until the blood has again reached the normal. So also the kidney removes urea from the blood and leaves sugar behind, though the blood normally contains four or five times as much sugar as it does urea. When, therefore, it became evident that the kidney removes egg-albumin at once and leaves serum-albumin behind, if the two varieties are presented to it side by side, the view was advanced that the freedom of urine from albumin depends upon a failure of the living renal cells to exert, in the case of serum-albumin, a secretory power which they exert in the case of egg-albumin. Or more exactly, it was held that the normal kidney-cells vitally excrete egg-albumin but resist the passage of serum-albumin.

Nussbaum's well-known experiment of tying the renal artery in the frog seems to show that in that animal, restraint of the passage of albumin into the urine is a function of the epithelium of the Malpighian tufts; for Nussbaum found that after ligature of these vessels, which supply the glomeruli, egg-albumin injected into the circulation is no longer excreted. But though a great advance has been made in locating the cause of the freedom of normal urine from albumin in the kidney, and perhaps especially in the Malpighian tufts, we are still ignorant of the true explanation of the phenomenon. The kidney can without doubt excrete egg-albumin, but could it, if necessity arose, excrete serum-albumin? In other words, we are still ignorant whether the freedom of normal urine from albumin depends upon a mechanical barrier presented by normal renal epithelium, or whether it depends upon the fact that under normal conditions the renal epithelium does not "choose" to excrete serum-albumin. If the first explanation be the true one, we should expect to find that albumin appears in the urine only when the barrier is broken down; if the second explanation be the true one, we should expect to find that under certain conditions the normal renal epithelium does "choose" to excrete serum-albumin. This brings us to our legitimate study—the pathology of albuminuria.

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[1] The values given for the amount of sugar that may be present in the blood without (easily recognised ?) glycosuria vary from ·5 (Saundby) to 3–4 (Stewart) per mille. Pavy reckons the amount as about 1 per mille., and probably he is most nearly correct. It must be remembered that the normal percentage of sugar in blood varies in different animals. The statement made in the text forms a part of the whole controversy concerning sugar and the fate of sugar in the body; it will be considered with diabetes mellitus.

Study of the pathology of the kidney having proceeded along with study of its physiology, the views that have been held with regard to the pathology of albuminuria have changed from time to time. When the freedom of normal urine from albumin was held to depend upon special properties of the "*filtering*" *fluid*, the presence of albumin in albuminous urine was held to depend upon an abnormal diffusion or filtration of albumin. There were two principal views upon this point.

On the one hand it was held that the albumin of the blood becomes changed in composition in diseases accompanied by albuminuria, and that owing to this change in composition the albumin filters easily through the kidney. This view was largely given up when it was found that the proteids of albuminous urine are the same as those present in normal blood, *i.e.*, serum-albumin and serum-globulin. Stokvis finally proved its inaccuracy by showing that when the albuminous urine of patients suffering from Bright's disease is injected into the circulation of normal animals, there is no escape of albumin by their kidneys. Senator held this view in a modified form; influenced by our knowledge as to the effects of dissolved salts upon the filtration of solutions of albumin, he considered that an unusual richness of the blood in salts, and especially in urea, might perhaps give rise to an escape of albumin into the urine.

On the other hand, it was held (and by a far larger number of authorities) that albuminuria depends upon an abnormality of the glomerular blood-pressure. At first this alteration was considered to be in the direction of increase, partly on the analogy of filtration experiments generally, and partly because there is evidence in many pathological conditions accompanied by albuminuria that the blood-pressure is raised. But after Runeberg had shown that, when an albuminous fluid is filtering through an animal membrane, the percentage composition of the filtrate in albumin varies inversely with the pressure under which filtration is taking place, there was a tendency to regard albuminuria as dependent upon a lowering of glomerular blood-pressure. Support for this view was afforded by the fact that albuminuria is a very frequent accompaniment of febrile and other diseases in which there is reason to believe that the blood-pressure is lowered.

But these views lost ground when it became recognised that the kidney itself exerts an important influence upon the composition of the urine. Henceforward albuminuria was regarded as dependent upon abnormality of renal epithelium (*the "filter"*), and this is the view held at the present day.

Though there are several points upon which there is not universal agreement, the modern explanation of albuminuria is fundamentally mechanical. The mechanical barrier presented to the escape of hæmal albumin by normal renal epithelium is broken down and the albumin is mechanically forced through a more permeable membrane.

The actual portion of the kidney which undergoes change and leads to albuminuria is, however, uncertain. In this connection we have to consider (A) the glomeruli, (B) the tubular epithelium, (C) the blood-vessels.

A. *The Glomeruli.*—Nussbaum's experiments would seem to indicate that it is the epithelium of the Malpighian tufts which is at fault in the production of albuminuria, and there is other evidence in favour of this view. Ribbert, having set up an artificial albuminuria in rabbits by intra-vascular injection of egg-albumin, excised the kidneys and placed them directly in alcohol so as to coagulate *in situ* the albumin within them; he found that the spaces of Bowman's capsules contained albumin as well as the tubules. Moreover, in very early nephritis following scarlatina, and in some other conditions, the glomeruli appear to be exclusively affected, so much so that Cohnheim suggested the special name of "glomerulo-nephritis."

B. *The Tubules.*—But it is very improbable that the glomerular epithelium is alone concerned in the process, though perhaps in some cases it is affected first and to the greatest extent. The cause which brings about the modification of renal epithelium and the supervention of albuminuria is in a large number of cases one that affects the whole circulation of the kidney. Thus, in the dog, if the renal artery is ligatured for an hour, there follows on loosening the ligature an albuminuria lasting perhaps for a week; in cholera, albuminuria accompanies recovery from the collapsed stage, in which there is often complete anuria from the lowness of blood-pressure; in cases of suppression of urine due to impaction of renal calculi in the ureters, if the flow of urine is re-established the fluid is albuminous; in cases of heart disease where tricuspid regurgitation has led to a general rise in systemic venous pressure there is albuminuria. In all these cases there can be no doubt that the epithelium of the tubules must suffer as well as the epithelium of the glomeruli. So also in nephritis the tubular epithelium must suffer; for when the irritant reaches the kidney by the blood it is conveyed through the blood-vessels to all parts of the kidney and not to the cortex, still less to the glomeruli, alone, and when the irritant reaches the kidney by the ureters and pelvis, as in consecutive nephritis, the medullary portion, *i.e.*, the tubules, must suffer first and most. Indeed there is evidence that the tubular epithelium may suffer alone, for Senator found, when he threw the kidneys of a rabbit into boiling water ten or twelve minutes after ligature of the renal veins, that it was easy to find masses of coagulated albumin and blood-corpuscles in the lumen of some of the straight tubules chiefly of the medulla, but that the spaces of Bowman's capsules were absolutely free.

It is possible, however, when nephritis is caused by toxic products of disease, and especially infective disease, that those portions of the kidney are most affected by which the irritant is specially excreted; thus it is possible that the scarlatinal virus is principally or entirely excreted by the glomeruli and that upon this depends the special form of nephritis associated with this disease. But nothing more than examination of a great number of sections from the same kidney is needed to convince one that even in acute nephritis the kidney is not everywhere affected alike. In one place the glomeruli, in another the tubules, in another the interstitial substance, may appear to be most involved, while some parts of a kidney, obviously pathological to the naked eye, may, by the microscope, be seen to be normal.

C. *The Blood-Vessels.*—But in discussing the pathology of albuminuria, besides the renal epithelium, one has also to consider the renal blood-vessels. The renal epithelium covering the glomerular blood-vessels and the renal epithelium lining the tubules may indeed be involved, in the production of nephritis for example, and it is conceivable that when they are affected albuminuria may result, though the renal blood-vessels, and in particular the capillaries, are totally unaffected; the capillaries elsewhere in the body give exit to an albuminous fluid under normal conditions, why not the renal capillaries?[1] But such a condition though conceivable must be infinitely rare if it ever occurs. In the production of albuminuria, vascular conditions must almost invariably, if not invariably, assist. For upon the vascular conditions and upon the blood which circulates in the vessels, the nutritive condition of the renal epithelium depends. So that in most cases vascular and renal epithelial changes must be twin results of the action of one irritant circulating in the blood, or the renal epithelial changes must be secondary to the vascular changes. We cannot imagine a vascular condition which is without its effect upon the renal epithelium, and can hardly imagine an alteration of the renal epithelium which does not depend upon some change in blood-vessels.

Now in the body generally, the capillaries, as the result of irritant action, give exit to a highly albuminous inflammatory exudation, so that it is not unreasonable to expect when the kidneys are the seat of inflammation, that the renal capillaries should also give exit to a highly albuminous fluid; the capillaries, too, not only of the glomerular tufts but also those surrounding the tubules. In the body generally this exuded fluid either remains stored up *in situ* or drains away by the lymphatics, and in the kidney also some of the fluid must be removed by the lymphatics which leave the organ at the hilum. But the kidney is enclosed in a firm fibrous capsule and cannot easily become œdematous, so that if all the exuded fluid cannot leave by these lymphatics it is highly probable that it will leave the organ by the tubules and constitute a part of the urine. In the glomeruli in particular it is difficult to see how any albuminous fluid that exudes from inflamed glomerular capillaries can fail to become mingled with the urine generally; and there is no difficulty in conceiving that fluid poured into the inter-tubular connective tissue may find its way into the lumen of the tubes. Hence in nephritis the fluid reaching the bladder would consist of urine *plus* inflammatory exudation.

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[1] The renal capillaries seem to be peculiar in one respect; the stomata which by appropriate staining are to be made out in most capillaries are very rarely seen in the capillaries of the kidney. This, of course, suggests a reason why ordinary lymph is albuminous, and normal urine free from albumin. More than this cannot be said, but the subject is eminently worthy of further investigation.

Moreover, we have definite evidence that vascular change is capable of producing albuminuria, for in lardaceous disease the glomerular vessels are often affected to a marked extent, and the urine is generally highly albuminous. It is true that in very early lardaceous disease the urine formed during life may have been free from albumin, though microscopic examination of the kidneys shows that the glomeruli are slightly but characteristically affected. But such cases are decidedly rare, and they do not affect the general statement made above.

In the case of mechanical hyperæmia (and of this nature is the chronic venous congestion of the kidney occurring in late heart disease), Senator definitely came to the conclusion that the lymph with its dissolved albumin and its suspended red blood-corpuscles transudes from the distended capillaries, finds its way into the urinary tubules and mingles with the urine. And Cohnheim in this respect is inclined to agree with Senator.

In nephritis, therefore, and in passive venous congestion of the kidney we must look upon the albumin in the urine—or part of it at all events—as bearing the same relation to the renal blood-vessels as does the albumin in the exudation fluid of an inflamed or a passively congested leg to the blood-vessels of that leg.

This being so, the question whether exudation in inflammation and in passive congestion is a physical or a vital process, which was discussed in Chapter VI., finds a new importance. For obviously, though from a somewhat different aspect, there arises once more the question: Is albumin present in albuminous urine because it is actively secreted or because the blood-vessels and the renal epithelium have become "more permeable"?

It is even more difficult to attempt an answer to this question than it was in the case of œdema-formation. For in the kidney we have to consider, not one membrane, but two, viz., vascular epithelium and true renal epithelium. In my opinion, however, the albumin of albuminous urine is secreted by the blood-vessels, but probably escapes into the tubules mechanically owing to actual lesions of the true renal epithelium. Nevertheless, when we remember that the normal renal epithelium excretes egg-albumin, we cannot deny the possibility that it may on occasion also excrete serum-globulin and serum-albumin; perhaps the so-called "physiological albuminuria" is of this nature. Moreover, there is no reason to doubt that the laws governing nutrition of the tissues generally are applicable also to the kidney, so that serum-albumin and serum-globulin must leave the vessels for the nutrition of the proper kidney substance, and must normally be restrained from passing into the urine by the integrity of the true renal epithelium. But whether this restraint depends upon vital or upon physical conditions is a question upon which we are completely ignorant.

Albumosuria and nucleo-albuminuria are probably more akin to the artificial albuminuria brought about by intra-venous injection of egg-albumin than to the albuminuria which we have just been considering. Albumosuria ("peptonuria") occurs especially in cases where large quantities of pus are pent up in the body, as for example in purulent meningitis and empyema, or where large masses of coagulated inflammatory exudation are undergoing liquefaction, as in the resolution of croupous pneumonia. In these cases it is probable that the albumose is taken up by the blood, and is excreted by the kidney as a useless and foreign substance.

Nucleo-albuminuria has only lately been recognised. It was found by Pickler and Vogt that in dogs intra-venous injection of a solution of casein leads to a nucleo-albuminuria lasting for a period varying up to five days. In one case they found it conjoined with ordinary albuminuria. Ligature of one renal artery for half to one and a half hour led in four dogs to a nucleo-albuminuria lasting two to seven days. Temporary closing of the renal veins led to a nucleo-albuminuria lasting three days, besides an ordinary albuminuria lasting one day. Von Friedländer investigated the urine of 100 male patients before and after chloroform-narcosis, and in forty-four out of fifty-six cases specially examined for the purpose he found a nucleo-albuminuria.

There remains a whole series of cases in which albumin is only at times present in the urine. Some of these appear to be of little importance clinically, but one at least—the albuminuria of pregnancy—is highly important, for the albuminuria itself is often so marked that the urine becomes solid on boiling, and cases in which the condition occurs not infrequently end fatally with symptoms like those of uræmia (puerperal eclampsia). Besides the albuminuria of pregnancy, this class also contains paroxysmal albuminuria to which sufficient reference has been made in connection with paroxysmal hæmoglobinuria, and the so-called "physiological" or "cyclical" albuminuria. Physiological albuminuria includes cases in which albumin is only present in the urine passed shortly after rising in the morning, cases of "digestive" albuminuria in which albumin appears in the urine after meals, and cases of the "albuminuria of adolescence," a doubtful condition which has principally been noticed in boys at the age of puberty.

The pathology of these forms of albuminuria is quite unknown. The albuminuria of pregnancy, it has been suggested, depends upon pressure involving the renal veins, and it has been noted that it is more common and more severe in first pregnancies;

but there are many objections to this mechanical view.[1] Cohnheim suggests that it is due to reflex spasm of the renal arteries, but this view is hardly more satisfactory. The most reasonable suggestion—unsatisfactory though it is—is that in certain persons functional power of the kidney is less stable than normal, so that in them balance is upset by circumstances that would be without effect upon persons with absolutely normal kidneys. It is doubtful whether any histological change accompanies physiological albuminuria, for the cases not proving fatal of course the kidneys cannot be examined. In the albuminuria of pregnancy, even when death has supervened from eclampsia, the kidneys may be apparently normal, though in some cases they show acute inflammatory changes.

(iii.) **The Substance discharged is FAT.**—The only important morbid conditions in which fat is discharged from the body are (*a*) those in which fat is removed with the fæces (steatorrhœa), and (*b*) chyluria, in which fat is removed with the urine.

(*a*) *Steatorrhœa.*—A certain amount of fat is normally present in fæces, and when an excessive amount is given by the mouth a very considerable proportion may pass through the intestines unabsorbed. The pathological presence of fat in the fæces is due to the fact that absorption from the intestines is hindered. The absorption of fat is contingent upon its emulsification, a process normally carried out by the combined action of the bile and the pancreatic juice. There are certain difficulties in the question to which reference will be made later, but there is no doubt that fat appears in the stools when the entrance of bile or of pancreatic juice or of both into the intestine is prevented.

Now the causes which lead to such a condition are essentially two, obstruction of the excretory ducts of the glands and destruction of the gland substances themselves. Of these, obstruction to the ducts is clinically by far the more important, for it is easily brought about, whereas destruction of the whole gland substance rarely if ever occurs (except as the result of experiment), and so long as a small functionating portion remains, the special secretion is formed. We therefore find that obstruction of the common bile-duct by a biliary calculus causes the appearance of fat in the stools (and jaundice, with which we are not now concerned), though the liver and pancreas are practically unaltered; but that, on the other hand, though the liver itself may be saturated with cancer and little of the pancreas may be normal, the stools remain comparatively free from fat so long as no nodule of cancer obstructs the biliary and pancreatic ducts.

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[1] That albuminuria is far more commonly seen in primiparæ is certain, but its explanation by pressure of the uterus on the renal veins is anatomically impossible. Of course we are not considering here pregnancy in persons who are already the subjects of renal disease.

Generally the condition which leads to the appearance of fat in the stools is one affecting the common bile-duct, one therefore which impedes the entrance into the intestine of both bile and pancreatic juice, but the absence of either secretion alone is effective. Since fat appears in the stools whether bile or pancreatic juice fails to reach the intestine, and since it will be necessary to consider bile in connection with jaundice, we shall deal here with the condition when it is caused by failure of entry into the bowel of pancreatic juice alone. This course is the more advisable, as our knowledge concerning food-changes after experimental extirpation of the pancreas has lately received considerable additions in connection with work upon glycosuria and diabetes.

Von Mering and Minkowski, Abelmann, Vaughan Harley, and others have all given experimental proof of the clinical fact first recognised by Bright in 1832, that in diseases of the pancreas large quantities of fat appear in the stools. Abelmann found that in complete extirpation of the pancreas 100 per cent., and in incomplete extirpation from 40 to 75 per cent., of the fat given by the mouth is passed in the fæces. Harley's results corroborate those of Abelmann. Harley further made some experiments upon a boy supposed to be suffering from obstruction of the pancreatic duct, and found that, when kept upon a strict milk diet, the patient passed about 75 per cent. of the milk-fat in his stools; a healthy man kept upon milk diet, as has been shown by Rubner, passes about 5–6 per cent. of the fat in his stools.

Now it is natural to suspect, when fat appears in the stools after obstruction (say) to the common bile-duct, that it does so because the fat taken in the food is not emulsified in the normal manner and therefore is unfit for absorption. This is the view that is commonly accepted and taught. It follows as a corollary that the fat in the stools should be practically identical with the fat taken by the mouth. But the quantitative estimations made by Harley seem to show that, whatever the cause, failure of emulsification cannot explain the condition, for the fat is not passed in an unaltered condition, but in a condition practically identical with that in which it is passed by normal animals upon the same diet. This is well seen in the following table, which is a condensation of two tables given by Harley.

*Table showing the average composition of fat in milk, in fæces of a normal dog, of a dog whose pancreas had been extirpated, and of a boy supposed to be suffering from obstruction of the pancreatic duct, in all of which the diet was milk alone.*

| | Neutral Fat. | Free Fatty Acid. | Soap. |
|---|---|---|---|
| | Per cent. | Per cent. | Per cent. |
| Average composition of fat in milk, . | 97·02 | 2·89 | 0·06 |
| Average composition of fat in fæces of normal dog, . . . . . | 34·17 | 58·65 | 7·19 |
| Average composition of fat in fæces of dog (pancreas extirpated), . . | 33·90 | 55·25 | 10·84 |
| Average composition of fat in fæces of boy with obstructed pancreatic duct, | 37·55 | 40·40 | 15·35 |

These figures show conclusively that the fault is one of non-absorption of fat and not one of failure to undergo change, for the neutral fat is broken up in the same way whether pancreatic juice is poured into the intestine or no. It will probably be found, however, on further investigation that the changes undergone by the fat are not identical in the two cases. Certainly the stools are markedly abnormal, for they are pale, soft, or oily, and yield a very foul odour. It is quite possible that when pancreatic juice is absent the fats are broken up by lipolytic ferments of bacterial origin and that the intestine is unable to absorb these, though it can absorb similar but not the same substances produced by the action of the lipolytic ferment of pancreatic juice.

(*b*) *Chyluria.*—The condition known as chyluria, in which fat is lost by the urine, is rarely seen in this country, and then practically always in persons who have resided in the tropics, particularly in Brazil, Mauritius, India, China, and the West Indies. It depends upon infection by an animal parasite known as *Filaria nocturna.*[1] In chyluria the urine is milky-white or pinkish or sometimes blood-red. The onset of the urinary condition is usually quite sudden, the peculiar urine being passed without previous warning, or perhaps after a period of retention due to intra-vesical formation of a coagulum and blocking of the urethra. Once chyluria has shown itself it lasts for a very variable period, extending to years, but commonly it is intermittent, and the appearance of the urine varies from day to day and at different times of the day. The relation of chyluria to the ingestion of fatty food is very remarkable and indicates the pathology of the condition. For the urine may be clear, but it becomes opalescent a very short time after ingestion of fat, as for example after a draught of milk. Chylous urine has a marked tendency to coagulate, but the tendency is very variable.

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[1] The filaridæ are nematode worms of which several genera are known, but of these only one—filaria—is parasitic to man. The most important species of filaria are *Filaria medinensis*, the "Guinea-worm," which is on an average 3 feet in length and inhabits the subcutaneous tissue of the lower limb, and *Filaria sanguinis hominis*, which is the cause of chyluria and other conditions. At least four or five different species of *Filaria sanguinis hominis* are known, the most important of which—from the fact that the embryos are only present in the blood during the night—is known as *Filaria nocturna.* The parent worms inhabit the lymphatic channels of the trunk and limbs, but the embryos circulate in the blood. The sexes are distinct. The male is about 70 mm., the female about 90 mm., in length ; both are filiform, white, smooth, and uniform in thickness, except towards the head and tail, where they taper somewhat. The embryos are born into the lymph in which their parents lie, and travelling by the lymphatics ultimately reach the blood. The embryos, which are far more commonly seen than the parent worms, and upon the recognition of which in the blood, diagnosis is generally founded, are about one-third of a millimetre long. They are actively motile and lie in a transparent sheath. Like most of the other entozoa, filaria requires an intermediate host for its full development, and it has been shown by Manson that the intermediate host for the filaria is the mosquito. It is impossible here to give the characteristics and life history of the parasite, but they will be found set forth in detail by Manson in his article on "Filaria" in Allbutt's *System of Medicine.*

Generally the urine coagulates rapidly into a solid mass after voiding, but sometimes flakes of coagulum only are formed and sometimes the urine does not coagulate at all. On standing, the clot shrinks and the urine shows a cream-like layer on the surface of the fluid expressed by the clot; the fat of the urine is present in this layer and in the clot.

Chyluria is essentially due to the fact that the normal course of lymph and chyle along the thoracic duct is impeded, or rather completely obstructed. The parent filariæ inhabit the thoracic duct and other lymphatic channels. Either mechanically by plugging the duct, or indirectly by inducing inflammatory changes in its walls, the parasites cause blockage of the upper part of the thoracic duct. For the passage of lymph and chyle from the lower parts—legs, pelvis, abdomen, etc.—anastomotic branches between the duct below the obstruction and above it have to be opened up, and in the process the already thin walls of the lymphatics become yet thinner. If, then, the lymphatics of the kidney or bladder are involved in the anastomosis, their rupture readily occurs, and the contents of the lymphatics mingle with the urine. Normally, of course, the lymphatics of the kidney and bladder do not drain the intestines, and the lymph in them is clear, so that when this lymph mingles with the urine, as it practically does in some cases of albuminuria, the urine is albuminous but clear. But under the abnormal conditions now being considered, the chyle in the intestinal lacteals passes upwards through these renal and vesical lymphatics, and, therefore, when they rupture, the fluid which is added to the urine is not pure, transparent lymph, but is lymph or chyle with the characteristics possessed by that fluid in the thoracic duct. Now the lymph obtained from the thoracic duct of a dog is a coagulable fluid, clear and transparent, and of a pale yellow colour or colourless when the animal has been fasting for twenty-four hours, opalescent or milky if he has lately been fed and especially if he has received fatty food, while it frequently has a pinkish or even a bright red colour under conditions which are not quite clear and are very variable. The evidence is therefore complete that chyluria depends upon admixture with the urine of chyle or lymph which normally travels by the thoracic duct.

It follows from what has been said that chyluria is only a special manifestation of a general filariasis, and that from rupture of dilated lymphatics elsewhere, fat may be lost to the body in this disease by other ways; chylous ascites, chylous diarrhœa, chylous hydrocele, chylous lymphorrhagia after rupture of a cutaneous lymphatic, have all been described.

(iv.) **The Substance discharged is SUGAR.**—In connection with this substance we have only to consider the urine, for though the saliva, tears, and sweat may contain sugar they only do so under the same conditions as those in which it is present in the urine.

Conditions in which the urine contains sugar may be divided into two classes: (*a*) those in which the sugar is only transitorily present, and (*b*) that in which sugar is more or less persistently present. The former class is known under the name of glycosuria, the latter is summed up in the disease known as diabetes mellitus, or, simply, diabetes.

It is, perhaps, normal for the urine to contain a minute trace of sugar, and where excessive amounts are taken in the food a certain amount of glycosuria may be present. Often the amount present is so small that it is uncertain whether the substance is truly sugar and not one of the many substances capable of reducing copper from its solutions with which small quantities of sugar are often confused. But in the pathological conditions of which we are about to speak, the amount of sugar is often so great that it is beyond the possibility of mistaken diagnosis, forming as it may do (in extreme cases) 10–12 per cent. of the urine and being excreted to the amount of half-a-pound or more, in the twenty-four hours.

The sugar present in the urine in glycosuria and diabetes is always pure dextro-rotatory glucose (dextrose), whether sugar has been introduced into the body as dextrose, cane-sugar, lactose, maltose, or whether it is due to ingestion of starch. When lævulose has been given by the mouth to diabetic dogs the major portion is excreted in the urine as dextrose (Minkowski), but small quantities of lævulose may be present in the urine also (Sandmeyer); the same is true also of galactose.

In glycosuria the abnormal urinary condition lasts only for a few days or, at most, weeks, and the amount of sugar excreted is usually small, though at times it may be as considerable as in a severe case of diabetes. Glycosuria may be caused by a number of medical and surgical conditions, some of which are serious, others trifling. Thus it often occurs after injuries to the brain, sometimes after injuries to the spinal cord, and rarely after injury to nerves; it is met with in patients suffering from carbuncle and boils, though the converse statement, viz., that diabetic persons often suffer from carbuncle and boils, is more generally true; it is said to be produced by the action of some poisons, notably strychnine, curare, morphia, ether, chloroform, carbonic oxide (though certainly in the case of some of these poisons the copper-reducing substance is not a sugar but glycuronic acid); it occurs in asphyxia and some other respiratory affections. During the actual time that a glycosuric person is passing sugar in his urine he presents—so far as that portion of his ailment is concerned—the same symptoms as a diabetic person. But from the shorter duration of the morbid condition and its, commonly, less severe character the symptoms are not so pronounced.

In diabetes mellitus the patient complains of great thirst and of frequent and copious micturition, for he often passes 10–15 pints of urine in the twenty-four hours. His appetite is voracious except towards the end of the disease, but still he wastes and becomes progressively weaker. His temper is irritable, his skin dry, his hair thin, his face flushed, his bowels irregular and often constipated, his temperature generally subnormal. He may suffer from impaired vision or actual blindness, the causes of which are various, and the impaired nutrition of his skin accounts for the many cutaneous disorders to which he is liable. If he be young his disease runs a rapidly fatal course and often terminates by way of pulmonary tuberculosis or of diabetic coma; if he be in early old age the prognosis is not quite so grave, though he may die of gangrene (generally involving the extremities) or as the result of that surgical interference which the gangrene necessitates. Whether young or old, since the resistance of diabetic patients of whatever age is far below that of healthy persons of the same age, he is very liable to succumb to any intercurrent infective disorder such as influenza or pneumonia.

The urine in diabetes is commonly increased in quantity, but if there be diarrhœa, a normal, or even less than a normal, amount may be excreted. The specific gravity is high in the great majority of cases (1025–1050) but occasionally it is low, and a specific gravity of 1008 does not preclude the possibility that the urine contains sugar. It has often a distinctive primrose colour and a characteristic sweetish smell. Besides sugar it contains an excess of urea and often deposits crystals of uric acid. Acetone, diacetic acid, $\beta$-oxybutyric acid, and $\beta$-crotonic acid are present or present in excess; they are important in that each or all of them has been supposed to be the poison which causes diabetic coma. Phosphates and ammonia are eliminated in great excess, indeed true phosphaturia may precede or coincide with diabetes. When diabetes has lasted some time albumin generally makes its appearance in the urine; this may depend upon accidental contamination with albuminous discharges, but more commonly depends upon a nephritis due to irritation of the kidney by the sugar. Histological changes of the kidney in diabetes have been described by Armanni, Marthen, and others; they consist in a hyaline transformation of the epithelium of the straight tubules and an epithelial necrosis in the convoluted tubules. Ehrlich showed that in diabetes the kidney epithelium contains glycogen; in health it is absent, and in other morbid conditions present only in minute traces.

The pathologico-anatomical changes found in the body of a person dead from diabetes are for the most part clearly secondary; but there are two varieties of change which we are probably justified in regarding as primary. These are (1) fibrotic and other changes of the pancreas, and (2) tumours and lesions in or about the medulla oblongata and the vagi.

Disease of the pancreas, though not always found in diabetes, is very common. Saundby gives the notes on this point of twenty-seven consecutive cases, in only six of which the pancreas was "normal." As a rule the organ is atrophied and fibrotic, more rarely it is enlarged. Morbid conditions in the neighbourhood of the bulb which can be regarded as primary are very rare, but they have undoubtedly been found. They may be tumours, or sclerotic affections extending into the bulb from the cord. It is noteworthy, however, in this connection that bulbar paralysis, a disease in which above all we might expect to find sugar in the urine upon the analogy of other cases and animal experiment, is not a cause of diabetes or glycosuria. Indeed Fagge doubted whether sugar has ever been found, though the urine has often been examined for the purpose.

The pathology of diabetes and glycosuria is obviously the pathology of either sugar-formation or sugar-consumption. For some reason the blood contains more than its normal percentage of sugar, and the excess is removed by the kidney. That when sugar is present in excessive quantity in the blood it is removed by the urine is readily seen by direct experiment, for when sugar (glucose) is injected into the jugular vein of an animal, the greater portion is within a short time recoverable from the urine, which is secreted in very large quantity. And that in diabetes there is glycæmia can be shown by quantitative analysis, for the blood may contain five or six times as much sugar as normal.[1] According to Vaughan Harley a dog can bear intra-venous injection of as much glucose as 1 per 1000 of his *body* weight without serious inconvenience if the kidneys be left untouched, but if the ureters are tied a far smaller amount than this leads to muscular spasms and coma.

At the present time no clear account of the pathology of diabetes can be given, but several facts are known which bear upon the question. First of all, however, we must consider briefly the origin and the fate of the sugar normally present in the blood.

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[1] Of course it is not necessary that in diabetes there should at any moment be a hyperglycæmia, for there might be glycosuria and yet the excretion by the kidneys might succeed in keeping the percentage of sugar in the blood down to the normal level. Seegen (cited by Levene) says that this is sometimes actually the case. *Cf.* also note, p. 605.

Claude Bernard showed that in the liver a carbohydrate substance—glycogen—is present, which can be readily converted into sugar. He therefore concluded that sugar reaching the liver by the portal vein, and derived from the food, is intercepted by the liver, converted into glycogen and reconverted into sugar, which is thrown into the circulation during the intervals between digestion. According to this view, therefore, hæmal sugar is of hepatic origin, and variations in the amount of sugar formed by the liver normally keep the percentage of sugar in the blood relatively constant.

Pavy, on the other hand, denies that the liver is a sugar-forming organ, denies that the changes undergone by glycogen in the liver after death are to be taken as an index of glycogen metabolism during life, denies that the hepatic vein ever contains more sugar than the blood of the general arterial or the portal systems. He regards hepatic glycogen as being a stage in the conversion of carbohydrate into fat, and looks upon the liver not as a sugar-forming but as a sugar-destroying organ. According to his view hæmal sugar is directly derived from the food and is sugar which has escaped destruction in the liver, or is sugar which, on the analogy of phloridzin diabetes, has been formed during the disintegration of proteid. The relative constancy in percentage of sugar in the blood in spite of variation in the amount thrown into it, he considers, is due to the efficient performance by the liver of its destroying function, and to the fact that normally the kidney removes an excess of sugar from the blood.

In spite, however, of the brilliancy with which Pavy has defended his theory, experiment and opinion at the present time are against him and in favour of the theory put forward by Bernard. The fact that Hahn and Nencki found no sugar in the urine of dogs, in which the liver had been thrown out of circulation by means of an artificial communication between the portal and hepatic veins (Eck's fistula), is weighty evidence against the view that the liver is a sugar-destroying organ. Nevertheless, it is probable that a certain amount of sugar normally passes directly from food to systemic blood without undergoing glycogenic change in the liver.

In considering the fate of sugar normally present in the blood we have only to deal with the actual destruction of sugar in the normal body. The old view put forward by Liebig, that sugar is oxidised in the lungs to carbonic acid and water, has long been given up, and at the present time it is held that the seats of sugar-destruction are certainly the tissues, and possibly the blood. There is reason to believe that sugar is used up in the metabolism of every tissue, but particularly in muscle. Though too much importance must never be attached to quantitative estimations of sugar in arterial and venous blood, there is a general agreement that the amount of sugar in venous blood is less than it is in arterial blood. Since normally the specific gravity of venous blood is higher than that of the corresponding arterial blood, it follows that the difference in sugar-content cannot depend upon a greater dilution of venous blood (for the contrary is actually the case), but that sugar must have been removed during passage of the blood through the tissue. This sugar must be consumed during muscular activity with the attendant production of carbonic acid and water. For when curare is administered, whereby the muscles are paralysed, excretion of carbonic acid by the lungs diminishes, and glycosuria occurs. Moreover, Seegen found that in animals, struggling (insufficient narcosis) and direct tetanisation of muscle diminish the amount of sugar in the venous blood by about 25 per cent.;[1] Chauveau and Kauffmann found that in one of the muscles of the upper jaw of the horse, three and a half times as much glucose was used up during activity (chewing movements) as by the same muscle during rest; and Morat and Dufourt and others have found in the dog that the glycogen normally present in muscle[1] undergoes a marked diminution during tetanisation.

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[1] This, however, is not the case when muscle is tetanised by stimulation of its nerve, for then Seegen found that the venous blood contains 15–40 per cent. more sugar than the arterial blood, a result which he ascribes to conversion of the muscle glycogen into sugar under the influence of nerve action.

Whether sugar is normally destroyed in the blood is somewhat uncertain, and it is difficult to say upon which side the balance of evidence lies. Many of the experiments that have been performed upon this point with blood *in vitro* are quite valueless, since there is no evidence that they have been carried out with asepsis, and growth of bacteria in the blood may well account for the destruction of sugar that has been noted in some cases. Vaughan Harley, however, has borne this objection in mind, and asserts that when blood outside the body is kept sterile, it still causes a progressive destruction of glucose added to it; this, he believes, is the result of ferment action. On the other hand, Arthus concludes from his experiments that no glycolytic ferment exists in circulating blood, but that it is derived in shed blood from disintegration of formed elements other than the red blood-corpuscles, and that it is a cadaveric phenomenon comparable with coagulation. The question would hardly be important from our present point of view were it not that Lépine has founded a theory of diabetes in which the absence of this glycolytic ferment plays a fundamental part.

In naming the causes of diabetes and glycosuria, reference was purposely omitted to three causes or groups of causes which are of extreme importance from an experimental and theoretical, as distinguished from a strictly clinical, point of view. Taking them in the order in which they will be discussed, these are ($\alpha$) puncture of the floor of the fourth ventricle in the region of the so-called diabetic centre and certain other lesions involving nerve-tissue; ($\beta$) extirpation of the pancreas; and ($\gamma$) poisoning by phloridzin, a substance derived from the root-bark of apple, pear, plum, and cherry trees.

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[1] It is doubtful whether we must consider the glycogen of muscle as being derived from hæmal sugar that is converted by the muscle into glycogen, or must regard it as being directly conveyed to the muscle as glycogen. There is no doubt that the blood normally contains glycogen both in the plasma and in cells (Liveriato, Gabritchewsky). The intra-globular glycogen is principally contained in the finely granular oxyphil cells (polynuclear, neutrophil cells), and the extra-globular glycogen is probably derived from disintegration of these leucocytes. The amount of glycogen present in the blood in disease is very variable. Liveriato found that in pneumonia, typhoid fever, empyema, and the acute fevers generally it is increased, but in acute rheumatism it is diminished, in jaundice only a small quantity of extra-globular glycogen is present; in diabetes (one case) intra-globular glycogen was completely wanting, extra-globular glycogen was almost wanting and in amount appeared to vary inversely with the glycosuria.

($\alpha$) We owe to Claude Bernard discovery of the fact that a definite but transient glycosuria follows puncture into the floor of the fourth ventricle in the neighbourhood of the vaso-motor centre. Shortly after puncture, the amount of sugar present in the blood is found to be doubled or trebled, and in about 30–40 minutes the urine is found to contain sugar. The maximum excretion of sugar occurs about one hour after the puncture, and from that time it gradually diminishes, disappearing after about five or six hours. Bernard, in his experiments on dogs, never found that it lasted for more than twenty-four hours. A similar glycosuria has been produced experimentally by operations on various regions of the brain, cord, and even nerves. Thus it has been observed after injury to the vermiform process of the cerebellum, after section of the cord at various levels but especially in the upper cervical region, after section of the splanchnic nerves, after destruction of the thoracic but more especially of the abdominal sympathetic ganglia, on stimulation of the right vagus, etc.

($\beta$) Though Lancereaux and others had pointed out that in diabetes the pancreas is frequently diseased, the experiments of investigators who ligatured the pancreatic duct or conveyed the pancreatic secretion outside the body through a fistula, led to results so little like those of diabetes that Cohnheim rejected the idea of a connection between the pancreas and diabetes, and regarded all pancreatic changes occurring in diabetes as "accidental complications." But the importance of the pancreas in some forms of diabetes at least was conclusively proved when von Mering and Minkowski showed that complete removal of the gland leads in dogs to a disease comparable in every respect with diabetes in man. The animal excretes an excessive amount of urine containing a large percentage of sugar (a dog weighing 7 kilos. may pass in twenty-four hours

1000–1200 c.c. of urine containing 70–80 gms. of sugar) and sooner or later containing also acetone, diacetic acid, $\beta$-oxybutyric acid, in fact all the constituents of diabetic urine. He eats and drinks voraciously, but wastes and loses muscular power nevertheless. The sugar in his blood increases markedly in amount, but the glycogen in his organs diminishes, and in his liver there may be only an imponderable quantity. After a short time (which never exceeded four weeks in the eighteen successful experiments of von Mering and Minkowski, and has been equally short in the numerous confirmatory experiments since published by many authors) the animal dies either from inanition or from lung trouble or from failure of the healing process. Extirpation of the pancreas, therefore, leads to exquisite diabetes. Nor is this result obtained in dogs alone, for the same authors obtained pancreatic diabetes in cats and in a pig. In rabbits they were less successful, owing to the great difficulties attending complete removal of the gland, but Hédon succeeded by inducing atrophy after Bernard's method of injecting oil into Wirsung's duct. Though von Mering and Minkowski failed with frogs, Aldehoff, and Markuse were successful, the latter in twelve out of nineteen experiments. With regard to birds, there appears to be a difference between grain-eating and flesh-eating species, for though Minkowski cites Langendorff as having produced the disease in flesh-eating birds, neither Minkowski himself nor other investigators have succeeded in producing an undoubted pancreatic diabetes in grain-eating birds.

For the certain production of diabetes, complete removal of the pancreas is necessary, though after incomplete removal diabetes will supervene if the intra-abdominal remnant of gland undergoes subsequent atrophy. In dogs, according to Minkowski, if four-fifths of the pancreas be removed the animal will sometimes manifest diabetes though of a less severe type. The delay before onset of diabetes after operation varies in different animals. Sandmeyer found that in dogs it appears immediately after operation and before the animals have received food, gradually rises during the next three or four days, remains at its maximum for a few days, and gradually diminishes till death occurs. In frogs Aldehoff and Markuse found that diabetes occurs on about the fifth day; and in rabbits Hédon found that it appears at earliest twenty days after injection of oil into the pancreatic duct, and is at its height between the thirtieth and thirty-fourth days.

Discussion of the method whereby removal of the pancreas leads to diabetes will be reserved till later, but it may at once be stated that the objection raised when first the experiment was made known, viz., that the result depends upon injury to the solar plexus or other nerves in the neighbourhood of the pancreas, is not a good one. For if a portion of the gland be transplanted beneath the skin of the abdomen and the rest of the gland be removed completely, no diabetes occurs, though it occurs immediately if the subcutaneous portion be removed later. That is to say, diabetes does not occur when there is possibility of severe nerve lesion and does occur after a small subcutaneous operation of no moment so far as nerves are concerned.

($\gamma$) Phloridzin-poisoning is highly important from a theoretical point of view, because the diabetes to which it gives rise differs somewhat from other varieties of experimental diabetes. It leads to the presence of sugar in the urine not by its own disintegration (though it is a glucoside) but by producing changes in the animal body whereby the animal's excretion of sugar is increased; for administration of 1 gm. of phloridzin will lead to the excretion of nearly 100 gms. of glucose in the urine. Phloridzin diabetes, according to most authors, differs from pancreatic diabetes in three important respects: (1) whereas hyperglycæmia follows extirpation of the pancreas, hypoglycæmia follows administration of phloridzin (this is denied by Pavy); (2) when pancreatic diabetes is at its height a further increase of sugar excretion can be produced by administering phloridzin; and (3) according to Minkowski no hyperglycæmia results in phloridzin diabetes if the kidneys are removed, whereas marked hyperglycæmia occurs under similar conditions in pancreatic diabetes. Phloridzin diabetes, too, is important in that it occurs under conditions in which participation of the liver in sugar-formation is impossible or improbable; thus Thiel found that it produces diabetes in geese after extirpation of the liver; Wolkow, that it produces diabetes after ligature of the hepatic duct has led to disappearance of glycogen from the liver; von Mering, that it produces diabetes when the liver has undergone marked fatty degeneration, a condition in which it fails to contain glycogen.

With regard to the method whereby phloridzin leads to diabetes we are at present uncertain. One view is that it simply increases elimination of sugar by the kidney, and this view is based on the belief that phloridzin diabetes is accompanied by hypoglycæmia. Minkowski suggests that the process is really confined to the kidney, that in this organ phloridzin is decomposed into phloretin and phlorose (a glucose), and that the phloretin combines in the organism with glucose to be again decomposed in the kidney.[1] But Levene found in some cases that the amount of sugar in the blood becomes diminished when phloridzin is administered after ligature of the renal vessels, and Cornevin showed that phloridzin greatly increases the amount of sugar excreted in milk; hence phloridzin cannot have a specific action on the renal excretion alone. The other view is that phloridzin leads to an excessive formation of glucose and that it produces the glucose at the expense of the body proteids; this view is probably the correct one, for the urine gives evidence of excessive destruction of proteid. Levene suggests that perhaps the change may take place in the kidney, for in eight out of nine cases he found that the blood in the renal vein contained more sugar than the blood in the artery.

With regard to the sugar-content of the blood in phloridzin diabetes, Pavy[2] controverts the statement that there is hypoglycæmia. He believes that sources of error occur in estimation of sugar for which allowance has not been made. By an improved method he estimated the sugar-content of the blood in eleven cats to which phloridzin had been given and always found a marked hyperglycæmia. Pavy further believes that the drug breaks up proteid, setting free a glucoside constituent, the existence of which in proteid he has attempted to prove by showing that sugar can be obtained from white of egg. It is probable, however, that this sugar is derived largely from ovo-mucoid; for it is now known that mucin yields copper-reducing substances allied with sugar if not actually sugar itself.

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[1] $C_{21}H_{24}O_{10}$ (phloridzin) + $H_2O = C_{15}H_{14}O_5$ (phloretin) + $C_6H_{12}O_6$ (phlorose); $C_{15}H_{14}O_5$ (phloretin) + $C_6H_{12}O_6$ (glucose) $= C_{21}H_{24}O_{10}$ (phloridzin) + $H_2O$.

[2] "Proc. Physiol. Soc.," *Journ. of Physiol.*, 1896, vol. xx.

*The Theories of Diabetes Mellitus.*—The theories that have been put forward to explain diabetes mellitus either lay stress upon an increased production of sugar or upon a diminished consumption; of these, theories belonging to the former class are the more numerous, and almost without exception they locate the seat of increased sugar-formation in the liver.

(1) *Vaso-hepatic Theory.*—After Claude Bernard had propounded the doctrine that normally the liver supplies sugar to the blood by the action of an amylolytic ferment upon the glycogen which it has formed from the carbohydrates of the food and has stored up in its cells, it was concluded that in diabetes we have an excessive formation of sugar in the liver. And after Bernard had further found that puncture of the floor of the fourth ventricle in the neighbourhood of the vaso-motor centre leads to hyperglycæmia and the presence of sugar in the urine, it was held that the excessive formation of sugar in diabetes depends upon an increased vascularity of the liver of vaso-motor origin.

This theory, which we may call the "vaso-hepatic" theory, though generally accepted, met with some opposition; it was severely criticised by Cohnheim. Cohnheim pointed out that there was no incontrovertible evidence that sugar is formed from glycogen, and that there is evidence, from the fact that the normal amount of sugar is present in the blood of animals fed on food free from carbohydrate, that the sugar in the blood may be derived from material other than carbohydrate, material which there is other evidence to show is proteid. Moreover, even if sugar be formed from glycogen there is no evidence that it is formed from the glycogen of the liver alone, since glycogen is widely spread throughout the animal body.

And lastly, even if the liver formed glycogen and the glycogen became hæmal sugar, he denied that there was any clinical or experimental evidence of increased vascularity of the liver, and maintained that in any case puncture of the fourth ventricle could not bring about such an increased vascularity with accelerated blood-flow as was supposed by supporters of the theory.

(2) *Glycolytic-ferment Theory.*—Though the vaso-hepatic theory did not gain Cohnheim's acceptance, he hesitated to deny the possibility of increased sugar-formation in diabetes, but modified the theory by adding the idea that there is diminished destruction of sugar. This diminished destruction he considered might be due to some defect in the liver,—for he readily granted that sugar absorbed from the intestinal tract is lost in the liver, and that in artificial (puncture) diabetes there is evidence of liver change in the loss of hepatic glycogen that occurs,—but on the whole he considered that diabetes depends upon "the absence of a ferment which in a normal condition initiates the further destruction of dextrose."[1] This, which we may call the "glycolytic-ferment" theory is largely held in an extended form at the present day.

(3) *Tissue-glycolytic Theory.*—Besides the view that insufficient glycolysis depends upon the absence of a ferment, a view to which reference will again be made shortly, it has been held that, in diabetes, oxidation in the tissues is diminished, so that less sugar is consumed than normal. This view, which essentially rests upon the observation that in diabetes there is an abnormally small formation of $CO_2$, has been supported by Ebstein and Van Noorden. In spite of assertions to the contrary, the bare statement that the production of $CO_2$ and the respiratory quotient are lower in diabetic persons than in healthy persons, is shown by Weintraud and Laves to be true. But this does not mean that the oxidative processes in the tissues are less in diabetes than in health, for such is not the case; it means that the diabetic patient, being unable to use sugar for thermogenesis, breaks down proteid and fat for the purpose.

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[1] Cohnheim, *loc. cit.*, p. 940.

Nevertheless, though these authors found in dogs made diabetic by extirpation of the pancreas, that the output of $CO_2$ and the respiratory exchange are much the same as in normal dogs, they found that in them administration of dextrose leads to a smaller rise of the respiratory quotient than it does in normal dogs. Van Noorden lays great stress upon this observation, as showing that in diabetes, sugar consumption in the tissues is diminished.

(4) *Neuro-secretory Theory.*—Besides the vaso-hepatic and the glycolytic theories, mention must also be made of a theory which may be designated the "neuro-secretory" theory of diabetes. According to this view the liver is supplied with definite glyco-secretory nerves which are independent of the vaso-motors. Though the existence of these nerves has not been anatomically demonstrated, it is an undoubted fact that lesion of nerve matter in certain regions is very liable to induce glycæmia and glycosuria. Further, Cavazanni found that stimulation of the cœliac axis increases sugar-formation in the liver, and Levenne found that stimulation of the peripheral end of the vagus has a similar effect.[1] So, too, Morat and Dufourt, starting from the fact that after section of the splanchnics, cerebral puncture does not lead to glycosuria, found (1) that stimulation of the peripheral end of the splanchnics in dogs increases the amount of sugar in arterial blood, and (2) that the glycæmia which follows on cessation of artificial respiration in curarised dogs does not take place if the splanchnics are cut. In a crude form the idea that diabetes is a disease of nervous origin is old, and depended largely upon the clinical experience that diabetes is liable to occur in persons who have lately been subjected to nervous worry or who have received injuries to the head. And Dickinson endeavoured to support this theory by the histological changes that he observed in the brains of diabetics. But the view

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[1] It is possible that stimulation of the vagus acts by way of the pancreas, for Pawlow found that vagus stimulation increases the external secretion of the pancreas, and Mett found that it leads to the appearance of pancreatic ferment in the otherwise ferment-free pancreatic juice of starving dogs.

that diabetes and glycosuria depend upon excitation of glyco-secretory nerves is a later development.

All these theories have undergone some modification since the time when von Mering and Minkowski demonstrated the importance of removal of the pancreas in causing diabetes. The vaso-hepatic theory, it is true, is now dead; but modified glycolytic theories and a modified neuro-secretory theory still claim their adherents.

*The Pancreas and Diabetes.*—The essential point of von Mering and Minkowski's observation lies in the proof it gives that the pancreas has an internal as well as an external secretion; it is the internal secretion which by its absence leads to diabetes. Controversy now turns upon the nature and the function of this internal secretion. Upon quite insufficient grounds it is generally assumed to be of the nature of a ferment, but questions as to its nature are insignificant in comparison with questions as to its function.

Lépine holds that the internal secretion of the pancreas is a glycolytic ferment such as that which Cohnheim supposed to exist. He found if the finely divided pancreas be digested for 2–3 hours with a ·2 per cent. solution of sulphuric acid in distilled water, then neutralised, and to the solution glucose be added and the whole be further digested for one hour, that about half the added glucose has been destroyed. This destruction Lépine believes is due to the fact that the acid converts a zymogen contained in the pancreas into glycolytic ferment. Normally, according to Lépine, the pancreas throws into the blood by way of the lymphatics a glycolytic ferment, the absence of which from the blood in animals from which the pancreas has been extirpated, allows accumulation of glucose in the blood and excretion of glucose by the urine. He asserts, further, that in the blood of diabetics there is less glycolytic ferment than in normal blood. We have already referred to the question whether normal blood contains a glycolytic ferment (p. 624), but though Spitzer allows that this is the case and that the glucose is oxidised to carbonic acid and water, he cannot confirm Lépine's statement that there is a difference between normal and diabetic blood in this respect. He found that the glycolytic power of the blood of five diabetic persons was about the same as that of healthy persons.

But other views are taken with regard to the function of the internal secretion of the pancreas. Chauveau and Kauffmann hold that the ferment influences sugar production. They cannot determine how it does this, but conclude that it does not act by way of the central nervous system, since Hédon has shown that cerebral puncture leads to a further increase of sugar in the urine of a dog from which the pancreas has been extirpated. They decide against the view that pancreatic diabetes depends upon a diminished consumption of sugar in the tissues, because they themselves found by quantitative estimation that the amount of sugar used up in the muscles of diabetic animals is the same as it is in normal animals, and because Weintraud and Laves found that the respiratory exchange and the respiratory quotient of diabetic dogs is the same as that of normal dogs. Dastre, working on asphyxia, also came to the conclusion that the glycæmia and glycosuria seen under this condition depend especially upon an increased sugar-formation in the liver.

Von Mering and Minkowski keep an open mind as regards the action of pancreatic internal secretion. They consider it possible that it may influence either the production of sugar from glycogen by its action on the liver-cells, or the production of glycogen from dextrose by its action on dextrose, or the tissues of the body so that they consume the dextrose form of sugar. Under any of these conditions absence of the internal secretion would lead to glycæmia and diabetes. Upon the first hypothesis because the hepatic cells would convert glycogen into sugar at an abnormally rapid rate owing to the absence of a restraining influence. Upon the second hypothesis because the liver would not receive from the food that form of sugar (perhaps lævulose) from which alone it can form glycogen, and the dextrose of the portal vein would pass into the general circulation and be excreted. Upon the third hypothesis because absence of the internal secretion would affect the tissues in such a way that they would no longer be able to use the dextrose form of sugar; normally, under the influence of a regulating mechanism, when there is need of sugar in the tissues, dextrose is produced by the liver and is used by the tissues; in the absence of pancreatic internal secretion, the liver under similar circumstances would produce dextrose as usual, but the tissues not being able to make use of sugar in this form, the dextrose would be excreted.

But though von Mering and Minkowski have added a fact of vast importance not only to our knowledge of diabetes but to the far wider question of internal secretions, and though clinical and experimental evidence are well in accord, we are still far from understanding the pathology of diabetes mellitus. That the pathology is not bound up with the pancreas alone is shown by the facts, amongst others, that cerebral puncture and administration of phloridzin lead to a further excretion of sugar in animals made diabetic by extirpation of the pancreas. Absence of the pancreatic internal secretion is an important cause, but it is not the only cause, of the appearance of sugar in the urine. Moreover, it is possible that the pancreatic internal secretion may act by way of the same mechanism as cerebral puncture and phloridzin, but it is manifestly impossible that cerebral puncture or phloridzin can act only by way of the pancreas and its internal secretion if they act through it at all.

Probably it will be found that we have here three different ways in which one condition which leads to glycæmia and diabetes can be brought about, just as shock, hæmorrhage, section of the splanchnics are three different ways by which one condition—fall of blood-pressure—which leads to a diminution of urinary secretion can be brought about. May has shown that in fever the consumption of proteid can be diminished by administration of glucose, a fact which suggests that in fever when glycogen throughout the body is greatly diminished, the necessary glucose is supplied in part or in whole by destruction of proteid. If this be so, and if, in fever, proteid is modified and converted into nitrogenous bodies and glucose, of which the glucose is used up by the tissues and the nitrogenous bodies are excreted, it is possible that by other and various causes not accompanied by fever the same modification and conversion of proteid is brought about, with the result that there being no especial use for the glucose, it, as well as the nitrogenous bodies, is removed by the kidneys. There would thus be produced the morbid condition which we recognise clinically as diabetes mellitus. Three facts are important in this connection: (1) when a diabetic person suffers from any intercurrent febrile disease the sugar in his urine generally diminishes in amount and often disappears altogether; (2) phloridzin leads to a diabetes which is accompanied by destruction of proteid; (3) bodies chemically allied to sugar, and, in some cases, true sugars, can be obtained from chondrin, mucin, colloid substances, which are widespread in the animal body, are closely allied to proteid, and into the last two of which we have ample evidence that proteid may degenerate.

More than this cannot be said at present, but clinically and experimentally there seems to be a fundamental difference between glycosuria and diabetes. An animal can only be made glycosuric by cerebral puncture or by injection of curare if its liver contains glycogen; such a condition is immaterial for the production of phloridzin diabetes or pancreatic diabetes. It is possible that the glycosuric animal excretes sugar derived from carbohydrate while the diabetic excretes sugar derived from proteid. Such a difference in origin would well accord with our knowledge as to the relative gravity of the two conditions so far as life is concerned.

In diabetes, when the sugar excretion has been brought to its lowest point by dieting, consumption of a single article of carbohydrate food leads to an increase in the output of sugar far exceeding the amount contained in the article of food itself. This fact has always proved a stumbling-block in the way of theories of diabetes. We have, it is true, a similar result in the case of phloridzin, and we know that when a fasting animal has reduced his nitrogen output to the lowest level compatible with life, administration of a single meal of proteid food leads to an increase of his nitrogenous output far exceeding the amount of nitrogen given in the food. In this last case we say that proteid is a stimulus to proteid katabolism, in the case of phloridzin we might say that the glucoside is a stimulus to proteid katabolism, and if the suggestion as to the proteid origin of diabetic sugar be true, we might say that in the case of diabetes, carbohydrate is a stimulus to proteid katabolism. This is the more probable since Ringer found that, in diabetes, ingestion of non-nitrogenous food is followed by a markedly increased output of urea as well as by an increased output of sugar. But in all these cases, though they have probably close analogies, the "explanation" given is no explanation, but only a periphrasis.

To sum up. We cannot as yet formulate one theory to explain all morbid conditions in which sugar is discharged with the urine. Nor can we positively say whether that excretion of sugar depends upon an excessive formation or upon a diminished consumption; but the weight of evidence is in favour of the view that excessive quantities of sugar are produced, and it is generally held that the seat of that excessive formation of sugar is the liver. There is evidence, however, which suggests forcibly that in phloridzin diabetes, in pancreatic diabetes, and in diabetes mellitus the sugar may be of proteid origin, in which case the seat of formation would probably not be confined to the liver. Nevertheless, the possibility even in these diseases that the sugar is of carbohydrate origin cannot be excluded.

**IV. Morbid Conditions in which Substances normally discharged are retained within the Body.**—The subjects that will be dealt with in this section are (i.) retention of fæces, (ii.) retention of urine and urinary constituents, (iii.) calculi. In the case of the first two it will often be necessary to distinguish between conditions in which the retention is relative only and those in which it is absolute, for the clinical features are generally very different in the two groups of cases.

(i.) **Retention of Fæces.**—Retention of fæces may be (*a*) relative (constipation) or (*b*) absolute (complete intestinal obstruction).

(*a*) In constipation the bowels act, but either the evacuations are too small or take place at inordinately long intervals, so that the fæces remain in the body for an abnormal length of time. Pollock records a case in which an action of the bowels took place once every three months; this is, of course, remarkable, but cases in which there is an action only once a week are by no means uncommon.

The causes of constipation are innumerable, but most of them may be included in one or other of the four following classes: (1) constipation from obstruction; (2) constipation from impairment of intestinal propulsive power; (3) constipation from abnormal consistency of the fæces; (4) constipation due to lowering of reflex irritability of the defæcation centre in the lumbar cord.

We cannot discuss these classes in detail, but the following particulars are sufficient to indicate the kind of condition included under each heading.

(1) Obstruction may come from within the bowel or from without. Thus it may depend upon new-growths of the intestinal wall or of neighbouring parts such as the uterus, upon inflammatory adhesions due to antecedent peritonitis, upon cicatrices in the gut, upon malposition of viscera such as a retroverted uterus, etc. Obstructive constipation very often ends in absolute retention of fæces.

(2) Impairment of propulsive power may depend upon weakness of the muscular coat of the intestine, or of muscles accessory to defæcation, *e.g.*, diaphragm and abdominal muscles. Thus constipation occurs in persons whose abdominal walls have been repeatedly stretched by successive pregnancies or by ascitic accumulation of fluid, and in persons in whom intestinal muscular power has been impaired by febrile disease[1] or by chronic over-distension of the gut, and so forth. Or it may depend upon impairment of nervous supply to the intestinal muscles; such, according to Lauder Brunton, is probably the

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[1] The constipation of peritonitis and perityphlitis which may and frequently does amount to absolute retention is of this nature, though probably reflex inhibition also plays a part. The intestinal muscles in these cases is exactly comparable to the muscle in the neighbourhood of an inflamed joint.

explanation of the obstinate constipation occurring in melancholia, mania, and cerebral disease generally.

(3) Abnormal consistency of the fæces may lead to constipation, because the fæces, when they reach the lower part of the intestine, are either so hard and dry that they cannot readily be forced onwards, in which case the condition approximates to obstructive constipation, or because they are so soft that they do not sufficiently stimulate the bowels to peristalsis. These conditions depend partly on the amount of water in the fæces, partly upon the physical characters of the solid constituents, factors which may obviously be varied by many conditions, of which alteration in the characters of the food taken by the mouth, alteration in the excretion of water by other paths than the bowels, alterations in the rate at which the intestinal contents travel along the gut, are the most important.

(4) Lowering of reflex irritability of the defæcation centre is a very important cause of constipation. In most cases it depends upon the fact that the reflex act of defæcation when called forth by the stimulus of fæces in the rectum is voluntarily and habitually inhibited, so that a kind of torpor of the reflex centre has been ultimately produced. This may depend upon sloth, misplaced modesty, the fear of pain induced by defæcation owing to the presence of fissure at the anus, etc., or upon many other causes. On the other hand, inhibition of the reflex centre may be involuntary, as for example when ovarian or uterine irritation leads to a constipation which disappears when the particular irritation is allayed. Or, again, the mechanism of defæcation may be included in a general weakness of nervous tone such as is summed up in the condition known as "neurasthenia." It is possible, too, in neurotic persons and in those who habitually use the higher functions of the brain that abnormal development of certain functions of the brain and spinal cord take place at the expense of others, and that in this way the mechanism concerned in defæcation may suffer.

The results of constipation are as varied as their causes; they may probably be referred in large part to absorption of toxic substances formed in the bowel by bacteria, but at present we know little as to the nature of these substances and still less as to the manner in which they act. In fact we do not even know whether the same substances are formed in constipation as in health. Sir Andrew Clark, indeed, suggested that the anæmia of girls is largely due to "copræmia," a name which he coined to imply that the blood is charged with substances of fæcal origin. But however probable this may be, we have no positive evidence that constipation alters the constitution of the blood. Many persons in seemingly perfect health have throughout their lives been the subjects of marked constipation. Acting as mechanical irritants, hard masses of fæces (scybala) may lead to the formation of "fæcal ulcers."

(*b*) Absolute retention of fæces only occurs in intestinal obstruction and in peritonitis. Of these conditions, too, it occurs especially in the acute varieties. It is necessary to draw a sharp line of distinction between (1) absolute retention suddenly produced and (2) absolute retention gradually produced, for the characters presented by cases of the two kinds are very different.

We may leave on one side consideration of peritonitis, for it presents no special pathological features in respect of retention of fæces that call for remark. But it must be noted that most of the symptoms seen in cases where there is absolute retention of fæces of sudden onset, are in large part due to the acute peritonitis which accompanies acute intestinal obstruction. This peritonitis depends upon infection by micro-organisms that have escaped from the bowel, sometimes through an actual perforation, more generally through the anatomically intact intestinal wall.

(1) Absolute retention of *sudden* onset is seen in its simplest form in acute intestinal obstruction occurring in a healthy individual. But it is also seen in patients who have suffered from constipation (or spurious diarrhœa) as the result of chronic intestinal obstruction. Sooner or later almost all cases of chronic intestinal obstruction end in absolute retention of sudden onset. Widely different, therefore, though acute and chronic intestinal obstruction undoubtedly are, in this point they agree.

Intestinal obstruction leading to absolute retention of fæces of sudden onset—in short, acute intestinal obstruction whether primary or secondary—unless relieved, terminates fatally within six or seven days. It is accompanied by profound shock (and later by collapse), by vomiting which ultimately becomes fæcal,[1] by pain, by diminution in the excretion of urine.

Concerning the *shock and collapse* we have already spoken. The *vomiting* is at first probably of reflex origin, such as that which accompanies conditions causing severe pain, *e.g.*, crushing of the testis, passage of a renal or a biliary calculus, dislocation of a semilunar cartilage in the knee-joint. Later it depends upon the increased peristalsis which occurs in the intestine above the seat of obstruction, and which, in obstruction low down, may be so marked as to be perceptible by the hand, or even obvious to the eye through the tense abdominal walls. In fæcal vomiting, the intestinal contents, and not, as in ordinary vomiting, the gastric contents alone, are ejected. At one time it was thought that fæcal vomiting depends upon a reversed peristalsis such as is seen to take place in the œsophagus in ordinary vomiting, but it is now generally taught that in intestinal obstruction the direction of intestinal peristalsis is unaltered, and that fæcal vomiting is brought about in the following way. Peristalsis acts to a greater extent upon the peripheral portions of the intestinal contents than upon the axial portions, and when the peripheral portions meet the obstruction, continued peristalsis forces them in the direction of least resistance, which is backwards in the axis of the gut towards the stomach. The *pain* of acute intestinal obstruction, often very severe, is partly due to direct injury of the intestine, partly to the peritonitis, partly to the forcible peristaltic contractions above the obstruction, and partly to mechanical distension from accumulation of putrefactive gases (tympanites). The *diminution of urine* is commonly said to depend upon the seat of obstruction, but this is denied by Treves, who holds that it depends upon "the acuteness of obstruction and upon the degree of impression made upon the nervous system."[1] It is certain that it must depend upon shock which lowers the blood-pressure and upon collapse which causes inspissation of the blood, for both of these conditions are eminently causes of diminished secretion by the kidney. But it is difficult to believe that the seat of obstruction is without effect, firstly, because Treves himself allows that the severity of shock and collapse in acute obstruction "is more marked in connection with the small bowel than with the colon, and in the lesser bowel it is the more severe as the stomach is approached";[2] secondly, because vomiting sets in earlier, is more persistent, and more copious the higher the seat of obstruction; and thirdly, because the higher the seat of obstruction the less is the amount of intestine available for absorption of fluid. All these conditions must conjoin in diminishing urinary secretion.

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[1] This statement is not absolutely correct; when obstruction occurs in the jejunum or upper part of the ileum the vomit can never be strictly "fæcal," though it may have an "intestinal odour." For the occurrence of fæcal vomiting in a strict sense the obstruction must be in the lower part of the ileum or in the large intestine; the contents of the lower part of the ileum are often little more than soft fæces, and regurgitation through the ileo-cæcal valve may, it is now allowed, take place during life. The statement made in the text is, however, sufficiently correct for our purpose.

(2) Absolute retention of fæces of *gradual* onset is only seen in cases of intestinal obstruction due to fæcal accumulation, and in them it is very rare. This condition is really an aggravated form of constipation in the popular sense of the word, and the symptoms observed in cases in which this variety of absolute retention occurs, are far less severe than those occurring when absolute retention is of sudden onset. If unrelieved, the case ends fatally it is true, but whereas patients in which onset of absolute retention of fæces is sudden, live for at most six or seven days, patients in which the onset of absolute retention is gradual, may live for weeks or even months. Treves writes of cases in which no motion was passed for fifteen weeks, eighteen weeks, seven months, and even eight months and a half. During this period the patient suffers discomfort, his tongue is foul, his abdomen distended, his mental condition becomes altered, he has foul eructations, nausea, and perhaps vomiting, and the vomit may become fæculent, but this is extremely rare. His symptoms, in fact, are similar to those of severe dyspepsia rather than to those generally found in intestinal obstruction.

It is not easy to explain the difference between cases in which the onset of absolute retention is sudden and those in which it is gradual. Probably it is peritonitis and shock that make the difference. One can imagine that where accumulation of fæces has been going on for years, the retained masses become so hard that even if perforation occur the chances of a generalised peritonitis by escape of intestinal contents into the abdominal cavity are small. Perhaps also in these cases the chronic constipation has led to a kind of active immunity to the products of bacterial action, so that when absolute retention occurs the individual is able to withstand doses which he could not otherwise have borne. But these are mere surmises. In any case the condition is important in that it shows clearly that the cause of death in intestinal obstruction of the ordinary kind is not due to mere failure of defæcation. Intestinal obstruction leads to other conditions beside which impediment to the passage of intestinal contents is insignificant; if death from intestinal obstruction were due to this cause alone, delay of a few hours in affording relief by surgical means would not be so dangerous as it undoubtedly is.

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[1] *Loc. cit.*, p. 843.

[2] *Loc. cit.*, p. 839.

(ii.) **Retention of Urine and Urinary Constituents.**—In the case of fæces it was impossible to distinguish between retention of fæces generally and retention of one or other substance normally discharged by the bowel. But in the case of urine it is not only to some degree possible, it is highly important. For we have to distinguish between (A) *retention* of urine, in which urine is formed but not discharged; (B) *suppression* of urine, in which it is a question whether urine is secreted by the kidney at all; and (C) *gout*, in which there is generally a plentiful discharge of urine but in which there is retention of uric acid.

(A) *Retention.*—Retention of urine occurs under two forms, obstructive and non-obstructive. The commonest but not the only causes of obstructive retention are, in men, stricture of the urethra and enlargement of the middle lobe of the prostate gland, in women, tumours of the uterus. The method whereby obstruction is produced differs in these cases. In men, the immediate cause of retention is usually congestion of the mucous membrane of the urethra or congestion of the prostate; in women, the immediate cause of retention is more commonly mechanical, the bladder being dragged upwards by the uterine tumour owing to the attachments between bladder and uterus, with the result that the urethra is elongated and forms a sharp bend above the pubes past which the urine cannot be forced. Non-obstructive retention (omitting consideration of hysterical retention) is of two kinds, that due to atony of the bladder wall and that due to paralysis. Atony may have originally depended upon obstruction, and in old persons hypertrophy of the prostate and atony of the bladder often conjoin to produce retention, but apparently it may also be independent of obstruction and depend upon senile atrophy or fibrotic changes in the bladder wall. Retention due to paralysis of the bladder occurs in diseases of the brain and spinal cord when the changes affect the micturition centre in the lumbar cord, either destroying it by including it in the disease or inhibiting its action for a prolonged period. In all cases where the patient is insensible the possible occurrence of retention must be borne in mind.

In all these conditions one has to distinguish between ($\alpha$) absolute retention and ($\beta$) partial retention of urine, for, speaking generally, absolute retention produces changes in the bladder alone, partial retention produces changes not only in the bladder but also in the kidney.[1] The reason of this lies in the fact that while absolute retention cannot last for more than a short time, partial retention may go on for weeks.

($\alpha$) In absolute retention the bladder is always dilated, owing to the continued secretion of urine by the kidneys, until the pressure in the bladder and ureters has reached a point which is unknown in man but which in the dog is about 60 mm. of mercury. The degree of dilatation, however, is not the same in all cases, as it obviously depends upon the degree to which the vesical wall yields before the increased pressure within the bladder; hence retention will not lead to so great a dilatation in the case of a bladder where obstruction has led to hypertrophy as in one in which there is atony. In the latter case the distended bladder may reach up to the umbilicus. The degree of dilatation will further depend upon pain; for where retention is painful, relief will be given either surgically or because the pain causes some movement of the patient which leads to rupture of the organ, long before distension has reached so extreme a point as it may easily reach (unless special precautions are taken) where retention is painless. It is hardly necessary to remark that painless retention occurs where there is interference with the passage of afferent impulses from the bladder to the brain, and that these are cases in which from the absence of hypertrophy the vesical wall offers little resistance to dilatation. Hysterical retention comes into this category. Absolute retention from obstruction, if unrelieved, ends in rupture of the bladder, non-obstructive retention in "retention with incontinence," hysterical retention in passage of a large quantity of urine, or incontinence, but never in rupture of the bladder.

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[1] Where absolute retention supervenes upon a long continued partial retention it is obvious that we shall find the combined effects of the two conditions.

($\beta$) In cases where retention of urine is partial, urine is discharged but the bladder is never completely emptied. Partial retention occurs in cases of prostatic enlargement where hypertrophy of the middle lobe of the gland, by projecting into the bladder, causes the formation of a pouch behind it in which urine collects that cannot be removed by micturition. It occurs practically in all cases where there is much obstruction to micturition from whatever cause, for the patient, having relieved himself of disagreeable sensations with great difficulty, is content and does not, like the normal person, take pains to eject the last drops of urine from the bladder. It occurs in cases of non-obstructive retention in which the pressure eventually attained by the urine in the bladder is sufficient to overcome the weak resistance of the sphincter. These cases constitute the class known as "retention with incontinence" or "distension with overflow." They are quite distinct from true cases of incontinence of urine. According to whether the bladder can or cannot overcome the resistance to the outflow of urine it hypertrophies or dilates, and therefore partial retention of urine may be met with in a hypertrophied, a hypertrophied and dilated, or a dilated bladder according to circumstances.

*Later Effects of Partial Retention.*—It is very rare for the urine in cases of partial retention to remain normal. Partly as the result of its mere presence, partly as the result of the condition upon which partial retention depends, changes occur in the bladder-wall. At first the mucous membrane pours out a little mucus, then it becomes congested and inflamed and cystitis sets in. Theoretically, perhaps, this cystitis might be aseptic, but practically the urine contains micro-organisms and undergoes putrefaction. Whether these micro-organisms gain entrance by the urethra in all cases it is difficult to say; in some cases they are introduced during catheterisation, in some it is possible that mucus extending from bladder to orifice of urethra is the path by which they travel upwards, and there is no reason why in some cases they should not have been derived from the intestine or vagina. But in any case they gain entrance to the bladder, multiply in the retained urine and induce or intensify cystitis. Even now they and the accompanying cystitis might perhaps be of comparatively little moment were it possible at frequent intervals to evacuate the bladder completely, but since the septic and inflammatory products collect and remain at the base of the bladder in the very region where the ureters open, infection readily extends by the ureters to the kidney. At first the ureters and the pelvis of the kidney are affected alone, but sooner or later the kidney substance becomes involved. As in every inflammation, the condition may or may not be accompanied by pus-formation.

But besides this mere spread of infection, another change must be mentioned. The condition upon which partial retention depends and the changes in the bladder to which it gives rise, have in most cases induced hypertrophy of the bladder-wall; for to the original trouble there has been added the fact that the urine contains much mucus, a substance more difficult to eject than simple urine. This hypertrophy presents an obstacle to the entrance of urine into the bladder from the ureters, for normally the ureters run for about an inch through the muscular and mucous coats before they open at the trigone, and when there is hypertrophy of the comparatively resistant muscular coat of the bladder this vesical portion of the ureter becomes elongated and compressed. As a result of this obstruction at their vesical end the ureters become dilated and tortuous; instead of having the diameter of a goose-quill they may have the diameter of small intestine. The pelvis and calyces of the kidney share in the dilatation, the pyramids are pressed upon and become atrophied, the cortex becomes thinned, and ultimately the kidney may be converted into a huge loculated cyst in which the presence of renal substance is with difficulty to be recognised. Add to this the fact that infection may or may not have reached the kidney, may or may not lead to pus-formation, and it is clear that with partial retention of urine, the kidney may present an infinity of different appearances, ranging between that in which it is almost normal and that in which it is converted into a dilated pus-containing sac (pyonephrosis, " surgical kidney ").

It may be mentioned in passing that renal changes similar in appearance and in pathology to those which have just been described may be caused by obstruction to any part of the urinary tract from the pelvis of the kidney downwards, *so long as the obstruction is not permanent and complete.* A calculus in the renal pelvis or the ureter, a stricture of the ureter which now and then becomes for a short time impassable, a kink in the ureter which from time to time allows passage of urine, may equally be the cause of any of the changes mentioned. When the renal dilatation is aseptic, the loculated sac is filled with urine, and constitutes a hydronephrosis. In the vast majority of cases where the primary trouble lies above the bladder, we have to do with the actual presence of a renal calculus, or the effects produced by passage of a renal calculus along the ureter. When the calculus is present in the pelvis of the kidney, pyonephrosis is more common than hydronephrosis, as it is in all renal conditions secondary to affections of the bladder or urethra; where, on the other hand, the renal calculus, having passed down the ureter, and there led to elongation, formation of scar-tissue, etc., reaches the bladder, and is rapidly passed by the urethra, hydronephrosis is more common than pyonephrosis.

(B) *Suppression of Urine or Anuria.*—In this condition there is failure to pass urine, because no urine enters the bladder from the ureters; it therefore differs widely from retention of urine.

The conditions upon which suppression depends are obviously those concerned with normal secretion by the kidney, and therefore they may have reference to blood-pressure, to the kidney-substance itself, or to the pressure against which secretion is taking place, *i.e.*, the essential factors governing normal urinary secretion. Clinically, suppression is said to be of two kinds—obstructive and non-obstructive—a distinction which is no doubt clinically useful, but which is pathologically unsatisfactory, since, as we shall see, it is doubtful whether some of the "non-obstructive" cases are not in reality "obstructive," though the obstruction is of a special kind. We shall therefore not adopt this classification, but shall divide suppression of urine into ($\alpha$) suppression in which the general blood-pressure is low, ($\beta$) suppression due to disease of the kidney, ($\gamma$) suppression due to increase of pressure in the pelvis of the kidney.

($\alpha$) *Suppression in which the General Blood-Pressure is Low.*—Bearing in mind the extreme extent to which secretion of urine—or, at least, separation of the water of urine—depends upon the blood-pressure, it is clear that anuria will occur whenever the blood-pressure in the glomeruli is below a certain point. What this point is, it is impossible to say, since we do not know the relations obtaining between glomerular and aortic blood-pressures. But there is no doubt that when the blood-pressure in the carotid of a dog falls to or below 30 mm. of mercury as the result of severing the spinal cord in the cervical region, or from other general cause, secretion of urine is almost invariably arrested.

There is no doubt that the anuria seen in shock depends upon the fall of general blood-pressure occurring in this condition, though whether fall of blood-pressure constitutes the whole explanation, we cannot say. Secretion generally is in so large a measure dependent upon nervous impulses, apart from those leading to vascular changes, that so long as we are uncertain whether the kidney possesses definite secretory nerves or no, dogmatism on this point is impossible. Suppression of urine may occur in shock from any cause, but it is more likely to occur the more severe the shock; hence it is seen especially where shock arises from perforation of stomach, intestine, uterus, and injuries of this description. Shock may perhaps also account for the anuria which is sometimes seen after operations on the urethra, or even after mere passage of a catheter.

In the suppression which may accompany collapse, lowness of aortic blood-pressure probably plays a part, for we have seen that in the later stages of collapse general blood-pressure falls rapidly. But it is possible that the anuria is, in part, an extreme manifestation of that diminution in secretion of urine which is noticed under all conditions in which large quantities of fluid are being removed from the blood by other paths. For in the early stages of collapse, anuria probably goes hand in hand with lowness of glomerular blood-pressure, apart from lowness of general blood-pressure. Anuria in collapse is seen to a marked extent in the collapsed stage of cholera, or in severe diarrhœa or hæmorrhage. An anuria of mixed origin may be met with in any case of severe peritonitis.

Suppression in which the general blood-pressure is low—the suppression of shock and collapse—of itself leads to no particular results: if the patient rallies, urinary secretion is re-established, and the urine is normal, or nearly normal, though it may contain for a short time a little albumin or a few blood-corpuscles. Where, however, the lowness of blood-pressure in the kidney has persisted for a sufficient length of time to bring definite renal changes in its train, alterations in the urine are more pronounced.

($\beta$) *Suppression due to Disease of the Kidney.*—This form of suppression differs in a marked degree from the form which has just been described. In the first place, the anuria does not go hand in hand with lowness of general blood-pressure, for, on the contrary, the general blood-pressure is almost invariably raised; and, in the second place, the suppression leads to a peculiar group of symptoms, known as "uræmia."

When disease of the renal substance itself leads to suppression of urine we have almost always to do with acute nephritis, whether it is primary or supervenes upon another renal condition. In these cases the suppression need not be complete; often a small amount of urine is passed, which is generally of high specific gravity (1025–1030), and contains blood-corpuscles and blood-, epithelial- or hyaline-casts. But this small amount of excretion does not greatly modify the progress of the case.

The actual diminution or suppression of urine in acute nephritis we must certainly ascribe to the inflammatory condition of the kidney; though how the inflammation acts is uncertain. Probably the retardation of blood-flow occurring in the vessels of an inflamed part is of great importance; indeed, Cohnheim ascribes the diminution in urinary secretion in all cases of nephritis to the retardation and the fall of blood-pressure which he says must accompany every inflammation. Probably, also, the casts which everywhere block the urinary tubules introduce an obstruction in the way of secretion that cannot be overcome. With this latter view, however, Cohnheim does not agree; "it is not because the casts occupy the tubules that the urinary secretion is reduced, but it is because the urinary secretion decreases that the casts are disposed to remain seated in the tubules." Nevertheless, it is difficult to understand how Cohnheim's view on this point can be correct, if we agree with him that the albumin in the urine is derived from the glomerular blood-vessels owing to their "increased permeability"; for, if the permeability be so far increased as to permit passage of albumin, it is reasonable to suppose that it would permit an increased and not a diminished flow of water. This, at least, is the case in inflammation elsewhere, whether we explain it after Cohnheim's fashion or in any other way. The problem is so complicated a one that it is not advisable to discuss it further here. For we not only commence with an uncertainty as to how far the water of the urine is a secretion, but also we add to this the uncertainty whether inflammatory exudation is poured out by mechanical or by secretory processes, and the uncertainty whether the fluid which leaves the kidney in nephritis is urine or inflammatory exudation or a mixture of both. It is quite possible that suppression may be due to the fact that the kidney is so disorganised in acute nephritis that for the time it is unable to secrete; it is quite possible that inflammatory exudation coagulates in the tubules, and prevents secretion; it is quite possible that these two conditions co-operate; between these possibilities and the one put forward by Cohnheim we cannot decide at present; there are arguments for and against each of them.

*Uræmia.*—Uræmia being a clinical term for a series of phenomena we shall follow clinicians, and divide it into "acute" and "chronic." In the acute variety these phenomena are epileptiform convulsions, accompanied by unconsciousness, vomiting, headache, and sometimes transient blindness. The convulsions are in all respects similar to those occurring in epilepsy; there may be one or many, or the patient may pass from one convulsion into another, until he is exhausted and rapidly dies. Unless urinary secretion be again established, death usually occurs in this way within two or three days; but where the secretion is not reduced to an extreme extent, or where it becomes re-established, recovery from an acute uræmic attack is possible. A convulsion may be the earliest sign of acute uræmia, but more commonly the onset of uræmic convulsions is preceded by vomiting and headache. The blindness of acute uræmia is remarkable in that it is very transient. It is almost always bilateral and complete, but it entirely disappears within a day, or at most a few days, and is generally unaccompanied by any ophthalmoscopic changes. In chronic uræmia, convulsions are much more uncommon. The patient complains of headache or giddiness, and he may become drowsy and apathetic, sometimes he may vomit, not infrequently he suffers from diarrhœa. This condition lasts for a variable time—days or weeks—and ultimately passes into coma, accompanied by marked dyspnœa ("renal asthma") and profound prostration. In such a condition the patient probably dies.

The onset of acute uræmia is almost invariably preceded by suppression or marked diminution of urine, and it follows, from what has been said above, that acute uræmia is especially associated with acute nephritis (primary or secondary). Chronic uræmia, on the other hand, though commonly associated with some diminution in urinary excretion, is not often associated with great diminution; it occurs chiefly in connection with fibrosis of the kidney (chronic granular kidney).

But whether there be suppression, diminution or no diminution of urine, acute and chronic uræmia agree in the fact that they are associated with diminished excretion of urinary solids, and, in particular, of urea and uric acid; the amount of these substances excreted per diem may be diminished to half or a quarter of the normal, or even less. On the other hand, bodies of the uric acid group other than uric acid itself (xanthin bases) are, according to Kolisch and others, always increased. The amount of urea in the blood is generally, though not always, increased, and may be two or three times as much as normal. These changes in urine and blood are most marked immediately before the onset of a uræmic attack; when the attack has passed, the amount of urea in the blood is found to have diminished.

*Theories of Uræmia.*—From what has been said in the preceding paragraph, it would seem that nothing could be easier than to produce an artificial uræmia in animals by intra-vascular injection of urea, but it is a well-established fact that the amount of urea in the blood may be artificially raised to an extraordinary height, and yet uræmia does not supervene. Nor is uræmia produced if large quantities of urine, or of blood taken from a dog made uræmic by ligature of the ureters, be injected into the circulation of another animal, though the symptoms are more severe than after injecting urea; for large injections of urine produce symptoms of poisoning, whereas injection of urea is without effect, unless the amount introduced into the circulation is truly enormous. This general absence of symptoms, and particularly of uræmia, is undoubtedly due to the rapidity with which the foreign substances are removed by the kidneys of the healthy animal, for under any of the conditions mentioned urinary secretion is greatly increased, and the urine contains an excess of urea. If the ureters be ligatured before urea is injected into the circulation, the result is different, for the animal after a few hours commences to vomit repeatedly (dog), or suffers from diarrhœa (rabbit), and in the course of a day or two dies in a comatose condition, after manifesting muscular twitchings or actual convulsions. But in this experiment it is ligature of the ureters that actually leads to the appearance of symptoms, and not injection of urea. This can be seen by ligaturing the ureters without subsequent injection of urea; identical symptoms are produced, and after the same lapse of time, so that injection of urea does not even hasten the event. It is said, however, that the effects are different when urine and not urea alone is injected after ligature of the ureters, for now vomiting and convulsions set in, and the animal dies comatose in about an hour and a half.[1]

But the fact that the urea of urine is diminished, and the urea of blood is increased in cases of uræmia, remains. So that, after it was found that simple retention of urea is insufficient to explain uræmia, Frerichs ascribed the condition not to the action of urea, but to the action of ammonium carbonate into which he supposed the urea was converted in the blood by a hypothetical ferment. This view he supported by showing that ammonia can often be detected in the breath of uræmic patients. This theory was at one time largely held, but it was abandoned after it had been shown that the ammonia present in the breath is due to decomposition of nitrogenous matter in the mouth, and is found in many conditions in which there is severe prostration, besides uræmia, and after Voit had shown that the only region in the living body where conversion of urea into ammonium carbonate takes place is the intestine, and that here it produces local effects only and not uræmia. Nevertheless, Voit found that when a dog is supplied with large quantities of urea in its food, and its supply of water is limited, the animal soon commences to vomit an ammoniacal fluid, and later shows great weakness and muscular twitchings, symptoms, in fact, in many respects similar to those of uræmia. These symptoms do not appear if an unlimited supply of water be allowed, and even if they have appeared, they may be removed by allowing the animal to drink freely. By some authors, therefore, it was still maintained that uræmia is due to poisoning with retained ammonium carbonate, though they shifted the seat of its production from the blood to the intestine.

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[1] The experiments to which reference is here made are those of Astaschewsky and Feltz and Ritter (cited by Cohnheim, *loc. cit.*, p. 1303). They are not convincing, for we have no evidence that the urine did not contain toxic substances of putrefactive origin, and even if the urine were aseptic, it was concentrated, and the mineral salts alone might account for the symptoms. This indeed Astaschewsky allowed, for, following Voit, he ascribed a considerable part in the production of uræmia to poisoning by mineral salts, especially those of potassium.

Attracted by the importance of the nervous phenomena in uræmia, other authors have propounded cerebral theories. Traube attempted to explain uræmia by concurrence of hydræmia and increase of arterial pressure in producing cerebral anæmia, a condition which it is well known may give rise to convulsions and coma. He supposed that when either hydræmia or arterial pressure is suddenly increased, the brain becomes œdematous and therefore anæmic. The occurrence of coma with and without convulsions, he ascribed to implication of different parts of the brain in the anæmia. But neither this view nor others which ascribed uræmia to meningitis, cerebral hyperæmia, etc., gained much acceptance at the moment, nor have they stood the test of time.

Pending further knowledge Cohnheim declined to single out any single ingredient of urine as the cause of uræmia, but ascribed it generally to retention of all the solid constituents.

At the present time the tendency is to regard uræmia as being dependent not upon urea, nor upon a destruction product such as ammonium carbonate, but upon an antecedent of urea.[1]

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[1] The relationship between the bodies to be discussed can be recognised by consideration of their structural formulæ. These are as follow: $\mathrm{CO}<^{\mathrm{OH}}_{\mathrm{OH}}$ = carbonic acid, $\mathrm{CO}<^{\mathrm{NH_2}}_{\mathrm{OH}}$ = carbamic acid, $\mathrm{CO}<^{\mathrm{NH_2}}_{\mathrm{NH_2}}$ = carbamide or urea. Urea may be formed by heating ammonium carbonate in a closed tube for several hours at 130°–140° C., $\mathrm{CO}<^{\mathrm{ONH_4}}_{\mathrm{ONH_4}}$ (ammonium carbonate) = $\mathrm{CO}<^{\mathrm{NH_2}}_{\mathrm{NH_2}}$ (urea) + $2\mathrm{H_2O}$. The same change occurs on heating ammonium carbamate, $\mathrm{CO}<^{\mathrm{NH_2}}_{\mathrm{ONH_4}}$ (ammonium carbamate) = $\mathrm{CO}<^{\mathrm{NH_2}}_{\mathrm{NH_2}}$ (urea) + $\mathrm{H_2O}$.

The most important work bearing upon the theory of uræmia that has appeared during recent years is that of Hahn, Massen, Nencki, and Pawlow. These authors investigated the effects of throwing the liver out the circulation by making an artificial communication between the portal and hepatic veins (Eck's fistula). They found that after the operation the animals (dogs) very frequently show nervous symptoms and change of character. Whereas formerly they were gentle and obedient, now they become bad-tempered, obstinate, irritable, restless, and liable to maniacal attacks and convulsions; their rate of respiration, too, is increased. This condition lasts for a variable time and is followed by depression of a comatose type. The animal refuses to rise when called, sleeps almost continuously, and if forced to walk, shows that co-ordination of muscles is impaired; it becomes blind and loses sensations of pain, but intelligence and hearing are unaffected. This state of depression often precedes another maniacal attack. During these attacks the animal often loses consciousness; attacks generally come on quite suddenly and are very likely to be fatal. They appear about the tenth day after operation, and their onset is closely bound up with administration of proteid food. Upon this latter point there is no doubt, and it has been corroborated by the observations of other authors. Besides these symptoms the animal may suffer from diarrhœa and vomiting. The clinical picture, therefore, is closely similar to that observed in uræmia.

Now the close dependence of maniacal attacks upon administration of proteid diet strongly suggests that the symptoms are due to absence of those metabolic changes occurring in the passage from albumin to urea and uric acid that are normally brought about in the liver. For though many of the arguments advanced in favour of regarding the liver as a urea-forming organ are not quite conclusive, there is still reason to believe that urea is chiefly formed in the liver. Assuming this to be the case, the authors mentioned next turned their attention to the urine and blood.

They found that the urine of their animals showed a diminution in the amount of urea, a constant increase in the amount of uric acid, which was less marked as the animals presented fewer subsequent symptoms, an increase in the amount of ammonia, which was often five or six times as great as normal, and a very considerable increase in carbamic acid. The ammonia was excreted as a carbamate. In the blood they found a salt of carbamic acid. Moreover, they found that injection of sodium or calcium carbamate into the blood or stomach of the operated dogs immediately calls forth symptoms of the depression type if ·25 gm. per kilo of body weight be given, symptoms of the excitement type if ·3 gm. per kilo or more be given. *In normal dogs none of these symptoms are produced, however much of the salt is given.* They therefore conclude that the symptoms are due to poisoning with a carbamate which, if the liver had been able to act, would have been converted into urea. For Schultzen and Nencki have shown that amido-acids (*e.g.*, leucin and glycocoll), which are obtained by hydration of proteids, when introduced into the body, are excreted as urea, and carbamic acid is (of course) an amido-acid.

The liver, however, is probably not the sole organ by which the conversion of ammonium carbamate into urea can be carried out, for even after almost complete extirpation of the liver, or when ligature of the hepatic artery is conjoined with formation of Eck's fistula, the urine still contains some urea, and the amount of urea in the blood undergoes no change. Hence there must be an actual formation of urea by parts other than the liver. Kauffmann came to the same conclusion, for he found that in starving dogs, though the blood only contained 32 mgr. of urea per 100 gms., the brain contained 86 mgr. per 100 gms., the spleen 62 mgr., muscle 64 mgr., *i.e.*, more than could be accounted for by the blood which they contained. There is some evidence, too, that the kidney itself may take a share in formation of urea from antecedents of urea.

The experiments to which reference has just been made might suggest the following explanation of the phenomena of uræmia. The symptoms of uræmia are not immediately due to the renal condition, but to the disorganisation of the hepatic function of forming urea from ammonium carbamate, which the renal disease brings about, owing perhaps to the absence of an internal secretion.[1] Ammonium carbamate, therefore, collects in the blood, and when a certain degree of concentration has been produced it acts upon the brain, with the result that convulsions, coma, etc., supervene. But the renal disease does not affect the power of muscle, etc., to form urea out of ammonium carbamate, and it is the urea of this origin that collects in the blood and causes the excess of urea that is noted before the onset of uræmic phenomena.

But there are many difficulties in the way of accepting this explanation of uræmia as it stands, not the least of which is the grave doubt whether urea is formed in muscle at all; general opinion is against ascribing this function to muscle, at least under normal circumstances.[2] Moreover, Rose Bradford found after he had removed the greater portion of both kidneys in an animal, that actually more urine containing more urea may be passed than before the operation: from this fact one would, *a priori*, conclude that in nephritis more urea would be formed and not less.

At this point we must leave the question, simply stating that uræmia probably depends rather upon accumulation of antecedents of urea than upon accumulation of urinary solids as such. What these substances are is unknown, but the experiments of Hahn, Massen, Nencki, and Pawlow forcibly suggest that one of them is ammonium carbamate which has escaped conversion into urea in the liver.[3]

(γ) *Suppression due to Increase of Pressure in the Pelvis of the Kidney.*—This form of suppression is of extreme interest in connection with the form last considered, in that the symptoms to which it gives rise are quite unlike those of uræmia. The patient is not dropsical, he does not usually vomit, he has no convulsions. He is drowsy and takes short snatches of sleep, but can be waked with ease, though he falls asleep again when his attention is no longer attracted. He may show a few muscular twitchings, but the principal symptoms besides the somnolence are failure to pass urine and feebleness of heart-action with a marked tendency to syncope. Unexpected syncope, indeed, is the common mode of death in these cases, but the patient lives nine to eleven days after the onset of complete suppression of this variety, whereas death occurs much earlier when complete suppression occurs in connection with nephritis.

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[1] *Cf.* p. 658 below. In this connection it is important to note that the symptoms of acute yellow atrophy of the liver—a condition in which disorganisation of liver substance is extreme—in many respects resemble those of uræmia; vomiting, convulsions, coma, and urine changes are present in both.

[2] Of course the accumulation of urea in the blood might be explained on the assumption that the liver does not lose the whole but only a part of its power to form urea; but this explanation does not suffice for experimental exclusion of the liver.

[3] Allusion will be made in the next section to the presence of urea in the vomit and sweat of uræmic patients.

The cause of suppression is almost always obstruction of one ureter by a renal calculus when the other kidney is disorganised by disease, but any condition or combination of conditions that can lead to sudden and complete obstruction of both ureters may lead to this form of suppression.

The pathology of this variety of anuria is, if possible, more uncertain than the pathology of uræmia. In both cases there is retention of substances (or their antecedents) which are normally found in the urine, and it is not easy to see why there should be a difference of symptoms. One suggested explanation is that a certain substance (or substances) normally found in the urine is partially formed in the kidney. If, owing to disorganisation of renal epithelium, this process cannot take place, antecedents of the substance accumulate in the blood and cause symptoms of uræmia; if, on the other hand, the fault lie not in the renal epithelium itself, but in excretion, the change takes place as usual, but the formed substance, being reabsorbed, collects in the blood, and not the antecedent. There is some evidence in favour of this view, for if a solution of kreatin be made to circulate through the vessels of the excised but still living kidney, urea is formed. But it is difficult to suppose that the ureter can long remain blocked without inducing changes in the renal epithelium itself, which would abolish its function. Moreover the effects of ligaturing the ureters in a dog approximate more closely to the symptoms of uræmia than to those occasioned by suppression due to impacted calculus. So that there are great difficulties in the way of accepting this explanation.

It is possible, however, that the kidney has an internal as well as an external secretion, and that it is the absence or presence of the internal secretion which accounts for the difference of symptoms in the two forms of suppression. This is the view that was held by Brown-Séquard; he and others found that when the kidneys have been extirpated, injection of an extract made of renal substance produces a notable return of vigour. Brown-Séquard supposed that there are three kinds of case: (1) those corresponding to total ablation of the kidney, in which both internal and external secretion are absent; (2) those corresponding to nephritis and other conditions, in which the kidney substance is profoundly altered; in them the internal secretion is absent or more or less altered, but the external secretion remains in part; (3) those corresponding to suppression from increase of pressure in the pelvis of the kidney, in which the external secretion is absent but the formation of internal secretion is intact. Since we have learned the importance of a pancreatic internal secretion there seems considerable plausibility in this view, but much investigation is necessary before we can decide whether it is more than a plausible hypothesis.

*Puerperal Eclampsia.*—Just as we do not know the pathology of the albuminuria of pregnancy so we are ignorant of the pathology of puerperal eclampsia. The symptoms are like those of uræmia, and the fact that eclampsia goes hand in hand with an albuminuria in which the urine is greatly reduced in quantity, inclines many authors to the view that eclampsia *is* uræmia. It is quite possible that this is the case, and if we are to regard uræmia as dependent upon absence of a renal internal secretion, we are to a large measure relieved of the difficulty that in some cases of fatal eclampsia the kidneys are apparently normal. We have a parallel in the case of diabetes, for though the pancreas is generally altered in fatal diabetes, in some cases it is apparently normal.

(C) *Gout.*—In gout we have a morbid condition in which the retention of uric acid within the body is clearly shown by its deposition from time to time in joints as a sodium salt. There is often no diminution in excretion of urine, or if there be diminution it is referrible rather to the fever which accompanies an attack of gout than to the gout itself. Nor is there necessarily a diminution in the amount of uric acid excretion, though such is generally the case; some authors have asserted that bodies of the uric acid group are invariably excreted in *excessive* amount in all stages of gout, but their statements have been denied. In any case, however, excretion does not go hand in hand with production, so that uric acid is heaped up in the blood. It has been repeatedly proved by quantitative analysis that the amount of uric acid in the blood is at its maximum immediately before an attack of gout and diminishes immediately after the attack has subsided. This, taken in conjunction with the fact that crystalline sodium biurate is actually found in joints that have been the seat of gouty inflammation, is sufficient evidence that gout depends upon retention of uric acid.

The sodium salt of uric acid deposited in gouty joints is a mortar-like substance, which microscopically can be resolved into a dense meshwork of acicular crystals. The substance appears to lie on the surface of the cartilage, but in reality it lies immediately beneath the articular surface. Its position in the cartilage is highly suggestive that it has been mechanically deposited from the synovia, for the feltwork of needles is densest in the most superficial portions of the cartilage and gradually becomes less dense as one approaches the bone. The salt is deposited in cartilage of other parts than joints, a very common situation being the ear, where it forms small accumulations ("tophi") on the helix. It is also deposited in fibrous tissue generally, but especially in the fibrous tissue found in the neighbourhood of joints; nevertheless, concretions may be found in the fibrous tissue of the palms and soles, eyelids, sclerotic, cerebral and spinal meninges, etc. In many cases it is deposited in the supporting fibrous tissue of the kidney, leading to formation of the "gouty" or "uratic" kidney; in the cortical portions of the organ the accumulations are scattered without obvious arrangement, but in the medullary portion they are arranged in lines running parallel to the vasa recta. In such an animal as the chameleon, which normally excretes nearly all its nitrogen as uric acid, the kidney sometimes becomes converted into a mortar-like mass in which very little of the original kidney substance is recognisable under the microscope.

The inflammation going on in a joint during an attack of gout calls for no special remark; it is simply an inflammation induced by a mechanical irritant.

But though arthritic manifestations are the most noticeable phenomena of gout they are not the only ones presented by a gouty person. Leaving out of consideration those manifestations which do not concern us, it may be pointed out that though an attack of gout may come on without warning, it is generally preceded by "premonitory symptoms." The patient is irritable or depressed, complains of headache and general dyspeptic symptoms —flatulence, acidity, loss of appetite, foulness of the tongue, palpitation, etc.; or he may suffer from neuralgia, irritating cough, cramps in the leg, etc. Since these symptoms come on at a time when the amount of uric acid in the blood is increasing and disappear immediately the arthritic attack is established, they may reasonably be supposed to depend upon the presence of uric acid in the blood. Slighter manifestations of this nature which do not culminate in arthritic attacks are not infrequent in gouty persons, or indeed in persons who have never suffered from gout but who have a strong family history of gout; they have been summed up under the name "lithæmia" or "uratæmia" (Roberts).

It is probable that, besides gout as it presents itself to the clinician, a great many slight indispositions not amounting to actual disease depend upon temporary overloading of the blood with uric acid or its congeners. Though one would perhaps not go so far as Haig, who considers uric acid accumulation as directly or indirectly accountable for a very large number of pathological conditions, it is in the highest degree probable that we have hitherto greatly under-estimated the importance of nuclein-derivatives generally.

The pathology of gout is bound up with questions as to the chemical combinations which uric acid can form in the body, and the solubilities of those combinations. These subjects have been studied with great care by Sir William Roberts, and the statements made in the following paragraphs are mainly derived from his article on "Gout" in Allbutt's *System of Medicine.*

Outside the body, uric acid can form, with each of the alkalies, a urate, a biurate, and a quadriurate. A urate can only be formed by the inter-action of uric acid with sodium hydrate, potassium hydrate, ammonium hydrate, etc., and since these substances do not exist in the body, normal urates cannot enter into the question of gout. Nevertheless, it is usually said that the material in gouty joints is "sodium urate," the deposit in uratic urine is a mixture of "sodium, potassium, and ammonium urates." The only salts with which we are concerned are the biurates and quadriurates.

In the blood and in normal urine, uric acid only exists in the form of quadriurate, a substance which is already sparingly soluble (1 in 500 of serum) and which in an alkaline medium takes up another atom of base and passes into biurate, which is almost insoluble (1 in 10,000 of serum). The mortar-like substance in gouty joints is sodium biurate. Conditions, therefore, which affect the solubility of sodium biurate and its formation from the quadriurate are of great importance in considering the pathology of gout. To these we shall now for a short time turn our attention.

*The Solubility of Sodium Biurate and its Formation from the Quadriurate.*—Though sodium biurate is only soluble to the extent of 1 part in 10,000 of serum, in pure water at 37° C. its solubility is about ten times as great. This difference in solubility apparently depends upon the presence of sodium salts in serum, for Roberts found that solubility of the salt in water diminishes in proportion to the amount of sodium chloride or bicarbonate in solution, so that, for example, in a ·7 per cent.

watery solution of sodium chloride, sodium biurate is almost insoluble. Moreover, if the salts be removed from serum by dialysis, it dissolves as much biurate as does pure water. Hence in the body deposition of sodium biurate will be more liable to take place according as the solution in which it finds itself contains more sodium salts. Roberts gives the following table showing the percentage of sodium salts in various fluids, tissues, and organs of the body, and it is remarkable that those tissues which are most liable to uratic deposit are richer in sodium salts than those which are less liable.

*Table showing the Percentage of Sodium Salts in the several Fluids, Tissues, and Organs of the Body.*

| | Sodium salts, per cent. | | Sodium salts, per cent. |
|---|---|---|---|
| Blood-serum, | 0·70 | Blood-corpuscles, | 0·20 |
| Lymph, | 0·70 | Brain, | 0.20 |
| Synovia, | 0·80 | Muscle, | 0·08 |
| Cartilage, | 0·90 | Spleen, | 0·04 |
| Fibrous tissue, | 0·70 | Liver, | 0·02 |

But sodium biurate exists in two forms, a crystalline and anhydrous (to which alone reference has hitherto been made), and a gelatinous and hydrated form which is very unstable and readily passes into the anhydrous crystalline form, but which is far more soluble in serum. In its passage to the crystalline biurate, sodium quadriurate passes through the hydrated variety of biurate, and the readiness with which this series of changes is carried out depends chiefly upon the amount of quadriurate present and the presence or absence of sodium salts. Roberts found that the series of changes takes place more rapidly the higher the proportion of uric acid (*i.e.*, quadriurate) in solution. Thus, in his experiments, when uric acid was present in solution to the extent of 1 in 3000, precipitation of biurate commenced on the third day, when present to the extent of 1 in 2000, precipitation commenced in thirty-three hours, when present to the extent of 1 in 1000, precipitation commenced in six hours. Similar experiments showed that the readiness with which crystalline biurate is precipitated from solutions originally containing quadriurate alone is hastened by the addition of sodium salts to the solvent, but is retarded by addition of potassium salts. At the temperature of the body, too, deposition of crystals occurs earlier than at the temperature of the room. As the result of all his experiments, Roberts concludes that an attack of acute arthritic gout can only take place when the synovia is impregnated with uric acid to the extent of about 1 in 2500. These facts indicate that an attack of gout occurs because the synovia and lymph are charged with quadriurate under conditions which lead to precipitation of crystalline biurate; the most important of these conditions being apparently high percentages of uric acid and of sodium salts in solution.

*Joints Affected in Gout.*—The fact to which reference has been made, that cartilage and synovia contain a greater percentage of sodium salts than lymph, blood, etc., probably accounts for the relative constancy with which joints are affected in gout and gouty conditions. But all joints of the body are not affected with the same frequency. The metatarso-phalangeal joint of the great toe is almost invariably the first to be attacked, and often it is the only joint affected; cases of arthritic gout in which it remains free are almost unknown. On the other hand, deposit of biurate in the hips and shoulders is less common, while in the maxillary, laryngeal, and sterno-clavicular joints it is excessively rare. The explanation of this fact is not quite clear, but it probably depends upon differences in freedom of circulation; in this connection it is suggestive that joints of the lower limbs are more liable to be affected than corresponding joints of the upper limb. To explain the frequency with which gout affects the metatarso-phalangeal of the great toe, Garrod laid stress upon its liability to slight injuries; he found that if any other joint has been injured, *e.g.*, the knee by a fall from horseback, it is liable to be affected before the metatarso-phalangeal joint, even though the injury may have taken place long before onset of the gout.

With regard to the slighter manifestations of the gouty state—which are non-arthritic—Roberts suggests that they may depend upon localised and inextensive deposition of crystals which are afterwards redissolved, for though sodium biurate is sparingly soluble it is not totally insoluble. He also calls in the aid of re-solution to explain the fact that joints which at some distant period were undoubtedly affected with gout, in some cases after death show a complete absence of uratic deposit.

*Source of Uric Acid in Gout.*—But even supposing the factors that have been mentioned are the immediate causes of deposition of sodium biurate in the joints—and upon this point there is not universal agreement[1]—we are still confronted by the question as to why uric acid (quadriurate) is stored up in the blood in gouty patients at all.

It is certain that gout is often associated with renal disease, especially of the fibrotic type, so that insufficient excretion may play some part in the process, but it is far more probable that there is an excessive formation of uric acid in gouty persons.

Now this excess of uric acid may be formed at the expense of urea. When we bear in mind the close chemical relationship between uric acid and urea, it seems possible to explain the condition by assuming that when nitrogenous metabolism has been arrested at a point of oxidation less than the normal (in which urea is formed), the result is uric acid. This seems the more reasonable since gout is especially liable to occur in persons who eat much nitrogenous food and take little exercise, conditions which one would expect to favour the production of a less highly oxidised end-product of proteid than normal. Seductive as this hypothesis is, it is doubtful whether it is altogether correct, especially in view of the different proteid origins which are now ascribed by many authors to urea and uric acid. Moreover, in gout and in the intervals between attacks of gout the excretion of urea is generally normal. Nevertheless, excessive consumption of nitrogenous food and deficient exercise are so often found in gouty persons that one is loth to deny that these factors may account for the accumulation of uric acid in the blood.

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[1] Pfeiffer believes that uric acid exists in the body fluids in a form not easily soluble and having a great tendency to precipitation, so that it is precipitated in the tissues, collects in quantities and leads to tissue necrosis. An acute attack of gout, according to this author, occurs when the alkalinity of the body fluids is increased and leads to a partial solution of the deposited uric acid. This view is, of course, diametrically opposite to that of Roberts given in the text. Von Noorden considers formation and precipitation of uric acid as a secondary process caused by the action of a local ferment and completely independent of the amount and relations of the uric acid formed in other parts of the body.

But it is by no means certain that the excess of uric acid in gout is derived from the ingesta at all. For more important even than excessive consumption of nitrogenous food, in the causation of gout, are alcoholic beverages, and in them nitrogen is practically absent; moreover, here we have not so much to do with an excessive consumption as with a moderate consumption of particular kinds of alcoholic beverages (port, sherry, madeira, sweet champagne, ale, and beer).

Now these beverages possess the common characteristic that they all contain a large proportion of sugar. We have seen, in the case of diabetes, that consumption of sugar leads not only to an excretion of sugar greatly exceeding the amount ingested, but also to an increase of nitrogenous excretion. So that it is possible that in gout also, sugar is a stimulus to abnormal proteid metabolism; the more so that an association between gout and diabetes is shown to exist by the facts that gout is not infrequently accompanied by a slight degree of glycosuria, and that diabetes mellitus may follow immediately upon an acute attack of gout. In the same way it is possible that, where gout is associated with excessive consumption of nitrogenous food, the uric acid is not derived from this food, but is due to an abnormal and increased tissue metabolism to which ingestion of nitrogenous food, like ingestion of sugar, may give rise. In a word, we do not know what is the proteid origin of the excess of uric acid present in the blood in gout; perhaps the fault lies, not in the ingesta, but in the proteids of the body itself, which are more liable to destruction than normal. Such a peculiarity might well be inherited, and the hereditary tendency to gout (and the same is true with diabetes) is one of the most striking characters of the disease. We shall probably be right, however, if we locate the immediate seat of uric acid formation in the liver.

*Lead and Gout.*—It has long been taught that there is a connection between poisoning with lead and gout, but it is doubtful whether the relationship is causal or only accidental. Opinions are divided upon this point, but the general opinion at the present day is that though lead-poisoning does not cause gout, it often leads to an attack of gout in a gouty person. Lead-poisoning when chronic certainly induces renal changes (chronic granular kidney), and perhaps in this way the connecting link is made, but it also induces hepatic changes, so that possibly nitrogenous metabolism in the liver is affected. Lüthje finds in dogs that intoxication with lead salts has no effect upon the excretion of uric acid, as most authors (following Garrod) believe. Even when the poisoned dogs are fed with thymus, which greatly increases uric acid excretion, the same is true. He therefore ascribes the gout of lead-poisoning to increased production of uric acid, and not to deficient excretion. Haig believes that in these cases an insoluble lead urate is formed. The effects of lead-poisoning, however, are so many and varied that it is useless to speculate upon the way in which lead-poisoning might lead to gout, so long as we are uncertain whether a direct connection actually exists.

(iii.) **Calculi.**—Under various conditions substances which are normally discharged from the body are retained and collect in masses, forming calculi or concretions. Leaving out of consideration gouty concretions and the concretions sometimes found in veins and arteries from calcification of thrombi, calculi are found mainly in the gall-bladder and biliary ducts, the kidney (and especially the pelvis), the bladder and prostate, the intestines, the salivary and the pancreatic ducts.

The composition of concretions varies considerably, but it is clear, from the work of Naunyn, Ebstein, and others, that in most cases, if not in all, they consist of an organic ground-substance, in the meshwork of which the inorganic substance is deposited. A calculus rarely is composed of one inorganic substance alone, and often it shows on section a stratified appearance, indicating that the layers of which it is composed have been laid down at different times. Thus a vesical calculus on section may show that the centre is composed of calcium oxalate upon which successive layers of oxalate and uric acid have been deposited alternately, while the whole is surrounded by a shell of mixed calcic and ammonio-magnesium phosphates. Calculi may be single or multiple, and different substances have somewhat different characteristics in this respect. Thus, the renal calculus formed of calcium oxalate is usually single, but several uric acid calculi are commonly present in the same kidney. Multiplicity is also a common characteristic of gall-stones; at times they may be present in scores. When more than one calculus exists in the same part, the stones are almost invariably faceted from mutual attrition or, more probably, from moulding while in a soft state.

Calculi in the intestines are usually gall-stones which have either been passed by the common bile-duct or have ulcerated into the intestine; besides them, however, "fæcoliths" are found in some cases. Fæcoliths are simple, hard concretions formed from some substance derived from the food. Calculi in the intestines do not call for special consideration from our point of view, though they are clinically of importance as occasional causes of acute and chronic intestinal obstruction, appendicitis, etc.

Gall-stones are commonly composed of cholesterin or a mixture of cholesterin and bile-pigment, but sometimes they consist of bilirubin- and biliverdin-calcium or of calcium carbonate. The reason for their formation is not quite clear, but probably it lies in a previous alteration of the mucous membrane of the gall-bladder or hepatic ducts. Naunyn holds that the conditions of their formation are (1) alteration of the mucous membrane, which leads to destruction and desquamation of epithelium and outpouring of mucus, and (2) stagnation of bile in the biliary passages; under these conditions bilirubin-calcium and cholesterin are precipitated in the organic material. On the other hand, Laves placed substances of great variety in the gall-bladders of dogs (irritating, putrefactive, alkaline, acid, substances and even gall-stones), but never found that they induced calculus-formation; in fact, small soft bodies disappeared, larger ones, if soluble, were dissolved in part, and if insoluble, remained completely unaltered. Mayer, too, inserted balls made of ivory, agar-agar, or clay, into the gall-bladders of dogs, and left them there for periods of not less than a year, but his results were completely negative as regards calculus-formation. However, gall-stones do not normally occur in dogs, so that the value of these experiments is perhaps somewhat diminished thereby.

It is not at all unlikely that micro-organisms are in a large measure responsible for the changes in the mucous membrane of the biliary passages which lead to deposition of substances from the bile and formation of gall-stones (assuming this to be the correct view); and the more so since Chiari, Sherrington, and others have shown that in typhoid fever, anthrax, etc., bacilli in pure or in impure culture are frequently found in the gall-bladder. Naunyn ascribes great importance to *B. coli communis* in causing changes in the mucous membrane of the bile passages. The views put forward by this author that bilirubin-calcium is precipitated from the bile when it contains calcium in excessive quantities brought to it by the blood, and that cholesterin is formed *in situ* from the epithelial cells, are probably correct.

Renal calculi are generally composed of uric acid or of calcium oxalate, but concretions formed of calcium phosphate, calcium carbonate, a mixture of calcium and ammonio-magnesium phosphate, cystin, xanthin, etc., are also known. The chief investigations made recently upon renal and vesical calculus-formation are those of Ebstein and Nicolaier and of Tuffier. Tuffier found that foreign aseptic bodies are in nowise altered by a sojourn in the normal urinary passages, and that the kidney or bladder which encloses such a substance undergoes no alteration due to the simple presence of this body. Nor is calculus-formation furthered under these circumstances, by giving a nitrogenous, phosphatic, uratic, or oxalate diet. Ebstein and Nicolaier produced artificial lithiasis by feeding dogs and rabbits with oxamide, an ammoniated derivative of oxalic acid, and Tuffier confirmed their results. He found, in addition, that lithiasis is more readily obtained if at the same time irregular foreign bodies are introduced into the urinary passages.

We have already discussed the conditions under which an excess of uric acid is formed in the body, and probably in the formation of uric acid calculi, whether uric acid is produced in excess or not, the conditions are much the same as in gout; indeed in gout it is very common to find small collections of crystalline uric acid in the urine as "gravel." With regard to the conditions under which calcium oxalate calculi are formed, it is doubtful whether passage of calcium oxalate in the urine is entirely a pathological process. Though the opposite view has been held, Dunlop and others believe that oxalic acid is a normal constituent of the urine of men living on a mixed diet; nevertheless, oxalate of lime is not always precipitated in the urine, though the amount of lime present is about twenty times as much as is necessary to precipitate the oxalic acid. Opinions as to the source of calcium oxalate are so conflicting, and our knowledge upon the whole subject is so scanty, that discussion of the subject here is impossible. It may be stated, however, that most authors hold that the oxalic acid is derived from vegetable food, and that its precipitation as a calcium salt is favoured by the presence of relatively large quantities of oxalic acid in solution. Chemically, however, it is possible that the oxalic acid is derived from uric acid.

Phosphatic calculi are occasionally found in the kidney, but more commonly in the bladder; they can, of course, only occur when the urine is alkaline. When a phosphatic calculus contains ammonium salts it must have been formed in a urine which was not only alkaline but had also undergone ammoniacal fermentation. Salivary and pancreatic calculi mainly consist of calcium carbonate; prostatic calculi, of calcium phosphate. But we shall not stop to consider these calculi. Nor shall we discuss the effects of calculi; though they are of extreme importance clinically, the symptoms, etc., which they produce are due to their mechanical action and call for no special remark in this place.

Under the heading of "morbid conditions in which substances normally discharged are retained within the body" ought rightly to be considered such abnormal conditions as imperforate anus, imperforate urethra, imperforate hymen, which are due to developmental defects, retention of portions of placenta, or even of the whole placenta, due to adhesions contracted between it and the uterine wall, retention of a dead and altered fœtus (lithopædion, etc.), even undue prolongation of pregnancy, and so on. But though these conditions are interesting and highly important, their discussion would take us beyond the scope of this work.

**V. Morbid Conditions in which Substances are discharged from the Body by Abnormal Paths.**—Though it is doubtful whether jaundice can rightly be considered under this heading, since it is perhaps hardly correct to say that bile or even bile-pigments are, as such, normally discharged from the body, it is convenient to assume as a fact the statement commonly made that bile is present in the fæces, and to consider, when bile-pigments are found in urine and sweat, that they are discharged "by abnormal paths." Jaundice, therefore, being the most important condition that we shall have to discuss in this section, its pathology will be dealt with first. Other conditions, which we shall afterwards have to mention, will not detain us long.

(i.) **Jaundice.**—In jaundice, bile-pigments, and in some cases, bile-salts, are discharged from the body by paths other than the bowel. They leave it in urine, in sweat, in inflammatory and other exudations. But though we have chosen—and with justice—to lay stress upon the discharge of bile or its pigments from the body, the most noticeable feature of jaundice, and the one from which it takes its name, is the presence of bile-pigment in the subcutaneous tissues. It is found nearly everywhere—the conjunctiva, the vitreous humour, the lungs, kidneys, fat, serous fluids, sweat (to take some examples) are all yellow. The brain and spinal cord, however, the liver in some cases, saliva, tears, gastric and pancreatic secretions, and mucus are free from pigment. The colour is not always yellow; when jaundice has existed for a considerable length of time (and, according to Fagge, when it has been dependent upon complete obstruction of the bile-ducts, but not otherwise) the bile-pigment in the skin undergoes oxidation as it does outside the body, and the colour gradually changes to an olive- or a dirty grey-green. The pigment is generally in solution, but in long-standing cases and in the jaundice of infants (*icterus neonatorum*) it is deposited anywhere in the body, but especially in the kidneys and fat, in a crystalline form. The wide distribution of bile-pigment in jaundice indicates that the pigment is conveyed to different parts by the blood, and when the plasma or serum is separated from the corpuscles, it is seen to be more or less deeply bile-stained.

The fact that bile-pigment is found in the blood, taken together with the fact that the most marked cases of jaundice are those in which there is obstruction to entry of bile into the intestine through the common bile-duct, early led to the recognition of a jaundice of obstructive origin. The obstruction may be caused by a gall-stone which has passed through the cystic into the common bile-duct, a gall-stone which has formed in the hepatic duct, a tumour of any kind which presses upon and occludes the common or hepatic duct, *e.g.*, carcinoma of the head of the pancreas or a gumma in the portal fissure, a catarrhal swelling of the mucous membrane of the duodenum or common bile-duct, and so on. In these cases it is assumed that bile is formed by the liver as usual, but being unable to escape into the intestine, it is reabsorbed, and enters into the blood either indirectly by way of the lymphatics and thoracic duct, or directly by bursting of the dilated bile-radicles into the blood-capillaries of the liver (Ziegler).

This form of jaundice was originally termed "hepatogenous," to distinguish it from jaundice in which no obstruction to the excretory ducts was found, in which the symptoms were often very different, and which occurred under conditions that, it was contended, imply a formation not of bile by the liver, but of bile-pigment in the blood itself; jaundice of this description was termed "hæmatogenous."

Even this division of jaundice into hepatogenous and hæmatogenous is only of comparatively recent origin (Kühne, 1868), for previously a division had been made into jaundice from obstruction and jaundice from non-elimination. Jaundice from non-elimination was so called because it was assumed that whereas bile-salts are formed in the liver, bile-pigments pre-exist as such in the blood, and are simply separated therefrom by the liver. But this view has been conclusively proved erroneous—so far, at least, as the general circulation is concerned—by the experiments of Kühne and others on frogs, and Minkowski and Naunyn on geese and ducks. These authors extirpated the livers of the several animals, and found that the animal does not become jaundiced, nor do bile-pigments accumulate in the blood, nor are they excreted in the urine. Hence a jaundice from non-elimination of bile-pigment, in this sense, does not exist.

Frerichs allowed that bile-pigment is directly formed by the liver, and attempted to explain cases of jaundice in which no obstruction to the bile-ducts is obvious, by assuming that they are accompanied by "polycholia." By this he meant that the amount of bile reabsorbed from the intestine is so great that a portion is unable to undergo its normal metamorphosis in the tissues, but circulates in the blood. He ascribed the greatest importance to the bile-salts in the causation of this "non-obstructive" form of jaundice, for he asserted that bile-acids can be directly converted into bile-pigment by the action of sulphuric acid outside the body, and showed that injection of decolorised bile into the circulation of animals leads to the appearance of bilirubin in the urine. It was soon proved, however, that the bile-salts of decolorised bile are not directly converted into bile-pigment, but produce bilirubinuria by acting upon the red blood-corpuscles; Kühne found in dogs that if he made an intravenous injection of blood colouring matter, he obtained hæmoglobinuria, whereas if he added a small quantity of a bile-salt to the injected oxyhæmoglobin, bilirubin appeared in the urine. We shall have to return to this question.

*Jaundice from Obvious Obstruction* ("*Obstructive*," "*Hepatogenous*" *Jaundice*).—We will first consider cases of jaundice in which obstruction is obvious, for their pathology is apparently simpler. Of the 1½–2 pints of bile which are normally thrown into the intestine during the twenty-four hours, some is probably reabsorbed, though how much it is impossible to say, since we have no information as to the quantity of hydrobilirubin necessary to give to fæces their normal colour, and we know that hydrobilirubin has smaller tinctorial powers than bilirubin (Gamgee). But taking for granted the general statement that bile is reabsorbed, there must be a great difference between the normal condition and the condition in jaundice from obvious obstruction. In the latter case, a large quantity of bile-pigment is thrown immediately into the general circulation; in the former case, such bile-pigment as is reabsorbed is absorbed gradually, and is probably carried at once to the liver by the portal vessels and there again worked up into bile, so that it never reaches the general circulation. According to this, which is the generally accepted view, jaundice due to obvious obstruction of the excretory ducts, depends essentially upon the fact that bile-pigment is thrown into the general circulation with abnormal rapidity, and in abnormal quantity, owing to failure of loss by the intestine. Besides bile-pigments, in this form of jaundice, bile-salts are thrown into the circulation, and their presence there is manifested particularly by the bradycardia that accompanies jaundice of this type. For when the bile-duct is obviously obstructed, the pulse rate may fall to 50, 40, or even 20 per minute, and production of such a result has been shown experimentally to depend upon poisoning by bile-acids.[1]

*Toxæmic Jaundice* (*"Non-obstructive," "Hæmatogenous" Jaundice*).—Jaundice which is not due to obvious obstruction of the excretory ducts of the liver, occurs under a variety of conditions, many of which are febrile. Thus it is seen in yellow fever, in remittent and intermittent fever, in pyæmia, in scarlatina, in typhus fever, in acute yellow atrophy of the liver, etc., with more or less regularity or rareness; it occurs as the result of poisoning by phosphorus, arseniuretted hydrogen, toluylenediamin (dog), and in some cases of snake-bite; it occurs sometimes after severe mental emotion or concussion of the brain. These forms of jaundice are further characterised by the fact that in most of them it is known with complete or tolerable certainty that a poison is circulating in the blood, and in many of the rest it is probable that a similar condition obtains. Moreover, in nearly all of the primary conditions upon which the jaundice depends, there is destruction of red blood-corpuscles. It was easy, therefore, to conclude that the jaundice in these cases depends upon a toxic destruction of red blood-corpuscles, and a conversion, *in the blood*, of the blood-pigment into the closely allied bile-pigment (hæmatogenous jaundice). This view, it was held, is supported by the absence in these cases of jaundice of that bradycardia which is characteristic of jaundice caused by the presence of fully-formed bile (*i.e.*, of bile-salts) in the blood; by the asserted absence of bile-salts in the urine; by the relative slightness of the jaundice in many cases.

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[1] Since bile-acids cause disintegration of red blood-corpuscles, in jaundice of this description there must also be an abnormally large formation of bile-pigment.

Now, there is no doubt that bradycardia is the rule in cases of "obstructive" jaundice, and the exception in cases of "non-obstructive" jaundice, unless it be due to some extrinsic cause; and no satisfactory explanation can be given of the difference. But it is certainly incorrect to say that in "non-obstructive" jaundice the urine does not contain bile-salts. For, in the first place, recognition of bile-salts in the urine is so complicated and difficult a matter, that assertions as to absence of bile-salts are not very reliable; and in the second place, Stadelmann found bile-salts in the urine in the "non-obstructive" jaundice caused by toluylenediamin, by phosphorus, by arseniuretted hydrogen; and Naunyn found them in two cases of pyæmia in which the hepatic ducts were free.

The view that jaundice in the cases under discussion is of hæmatogenous origin has been opposed with great force. Stadelmann, following up Schmiedeberg's observation that toluylenediamin produces an intense jaundice in dogs, found that in these animals injection of the drug leads to the following changes: From the 2nd to the 14th hour after injection, the bile is very rich in pigment and is excreted in increased quantity; from the 14th to the 60th–70th hour, nothing but a small quantity of colourless mucus is formed; later, and gradually, excretion of characteristic bile is re-established. Jaundice commences in the first stage, is at its height in the second, disappears in the third. Bile-pigment is present in the urine from the first, but bile-acids do not make their appearance till about the middle of the second stage, and about twenty-four hours later they may be present in the urine in considerable quantity. Now, Stadelmann was unable to find any evidence of duodenal catarrh, and until Afanassiew had shown that the drug causes great destruction of red blood-corpuscles he did not recognise this point. Hence, at first, he was unable to offer any explanation of the jaundice, but after he had fully confirmed Afanassiew's observations he concluded that the explanation is as follows: The drug causes blood destruction, and the freed hæmoglobin leads to an increased formation and excretion of bile-pigments, which is attended by an increased viscosity of the bile; in face of the low pressure at which bile is secreted, this increase of viscosity offers a temporary obstruction to the onflow of bile and leads to its reabsorption. W. Hunter carried the matter further and found that the concentration of the bile, which is so marked, is due to an extensive catarrh of the bile-ducts extending from their origin downwards towards the duodenum. This catarrh is occasioned by excretion of the drug or its derivatives in the bile, for Hunter determined the presence of the poison in the bile as early as one hour after its subcutaneous injection.

It follows, therefore, that jaundice after administration of toluylenediamin—a jaundice which appears at first sight to be eminently "hæmatogenous"—is really due to obstruction of the bile-ducts. In the case of poisoning with phosphorus and with arseniuretted hydrogen, Stadelmann obtained, essentially, the same results as with toluylenediamin.

Minkowski and Naunyn gave an even more conclusive proof that the liver is necessary to the production of so-called "hæmatogenous" jaundice. Having found that poisoning with arseniuretted hydrogen leads, in geese and ducks, to destruction of red blood-corpuscles and to the presence of bilirubin in the urine, they proceeded to extirpate the liver, in some cases before, in some cases after, submitting the birds to action of the gas. They found that in the absence of the liver, though hæmoglobin is present in the urine, bilirubin is always absent.

As a result of these experiments and others of a similar kind, it is now generally, though not universally, held (1) that a hæmatogenous jaundice does not exist; (2) that all varieties of jaundice are hepatogenous and due to reabsorption of bile formed in the liver; (3) that re-absorption is due to the presence of an obstruction in the bile-ducts, whether this obstruction is obvious—*e.g.*, a gall-stone—or not. Jaundice, therefore, only occurs as the result of blood destruction, when the liver seizes on the blood-pigment, converts it into bile-pigment, and returns it in bile to the blood.

*Infantile Jaundice.*—Opinions are very divided as to the exact way in which infantile jaundice is brought about, though most authors ascribe it to changes in the hepatic circulation occurring at birth. Frerichs thought that it depends upon a diminution of tension in the capillaries of the liver which leads to a transference of bile into them. Birch-Hirschfeld regarded it as being dependent upon an œdema of Glisson's capsule, due to venous congestion in the region of the intra-abdominal portion of the umbilical vein and the portal vein. Ziegler believes that after birth, bile-pigment is formed in large quantity afresh, and is absorbed also in large quantity from the meconium. Neumann finds that at birth, in many otherwise normal children, a certain small amount of bile-pigment, not sufficient to lead to a true icteric coloration, is present in the blood and in the tissue-juices in solution.

(ii.) **Fistulæ and other Conditions.**—Concerning other morbid conditions in which substances are discharged from the body by abnormal paths so little need be said that they may be considered under one heading. The most important is that in which the secretion or excretion is discharged through a fistula. Fistulous conditions may be due to developmental defects, as, for example, when urine escapes at the umbilicus through a pervious urachus; or they may be artificially made by the surgeon, as, for example, in the operation of colotomy for intestinal obstruction, or suprapubic puncture of the bladder for retention of urine. But far more commonly fistulæ and fistulous communications are the result of ulceration, whether due to action of an irritant or occurring in a malignant new-growth. As the result of ulceration (and abscess-formation) a great variety of conditions may be met with; gastric contents may be passed directly into the colon, owing to fistulous communication between these two viscera; bile may be discharged from a biliary fistula, owing to adhesion of an inflamed gall-bladder to the abdominal wall, abscess-formation in the inflammatory material and discharge of the abscess outwards; intestinal contents may be discharged in small quantity through the abdominal wall, owing to similar changes resulting from appendicitis; fæces, flatus, or urine may be passed by the vagina, owing to ulceration of a carcinoma, which starts in the uterus and involves either rectum or bladder, and so on. In the most common form of fistula—fistula in ano—though the bowel communicates with the exterior by an opening other than the anus, intestinal contents do not escape by the fistula owing to its narrow lumen.

Under this heading, too, comes the discharge of urea in sweat and vomit that occurs in uræmia: though the amount is not great, a recognisable quantity of urea may be removed by these paths. Urea may also be discharged by the sweat in other morbid conditions. In acute rheumatism, according to Harnack, about half of the organic material of the sweat is urea, and with profuse sweating as much as 1 gm. of urea may be given off in this way in an hour.

In intestinal affections, especially intestinal obstruction, substances of the indigo series (indigo, indican, indol, skatol), which are normally removed by the bowel, may pass into the urine. Rosenbach finds that substances of this group are present in the urine in three classes of case: (*a*) in severe intestinal affections, or immobility of the intestine from any cause, or when the power of intestinal absorption is deficient; (*b*) in very severe diarrhœa, from whatever cause; (*c*) in the cachectic terminal stages of chronic diseases, *e.g.*, pulmonary tuberculosis and carcinoma. There is no doubt that the substances in question are produced in the intestine by the action of bacteria on proteid.

Lastly, we have those doubtful cases in which a "vicarious" discharge is said to occur. Most of these are connected with menstruation, and a periodic discharge of blood from the nose, lungs, bowel, etc., is said to take the place of normal menstruation. These cases of "vicarious menstruation" almost always occur in hysterical individuals and are open to criticism, but in a few, a truly vicarious flow of blood may apparently occur. Of course, in a strict sense, excessive secretion of sweat may be called a "vicarious" secretion of urine, especially if the sweat, as in uræmia, contain urea; but cases such as these are not understood under the name.

**VI. Morbid Conditions in which the Secretions or Excretions contain Substances not normally present in the Body.**—The morbid conditions which are to be included under this heading are varied and important. They include all forms of infective disease in which bacteria or their toxins are eliminated by the urine or other secretion, all forms of poisoning by drugs,—and even morbid conditions in which drugs are given with a therapeutic object, where the drug is found in the secretions or excretions,—all forms of disease caused by parasites in which the parasite is found in intestinal evacuations or urine. It is impossible to discuss these conditions here, and it is unnecessary, since they are considered fully in clinical treatises. But it may be pointed out that, though the abnormal substance is generally to be looked for in the urine, other secretions and excretions are not exempt. Thus typhoid bacilli are often to be found in the bile (Chiari) and urine (Horton Smith), as well as—though with difficulty—in the stools; anthrax bacilli may be found in the stools, but often also in the urine.

In almost all cases presence of a given micro-organism in several secretions or excretions implies that the micro-organism has gained access to the blood, but it must be remembered that there may be multiple seats of local infection. Thus, when a patient with gonorrhœa infects his conjunctiva, the urine and conjunctival fluid both contain gonococci, and when a patient with tuberculosis of some part of the genito-urinary tract also suffers from pulmonary tuberculosis, his urine, semen, expectoration, contain, or may contain, tubercle bacilli; but in the second of these examples there is not necessarily hæmal infection, and in the first it is expressly excluded.

When, in infective disease, micro-organisms are found in the urine it is not certain whether they have been actively excreted by the uninjured kidney, or whether they have merely escaped through a damaged renal epithelium. It is, of course, impossible to compare micro-organisms with the solids of urine, since these are secreted in solution and for the most part remain in solution; and even when crystalline uric acid and calcium oxalate are found in the urine the crystals have been formed on the distal side of the renal epithelium. Sherrington found that when the blood is teeming with micro-organisms, there may not be the slightest transit of them into the urine; moreover, he believes that they may appear in the urine though no blood escapes by the kidney. Nevertheless, he holds that the kidney is probably not normal, and that the lapse of time between injection of bacteria into the blood and their appearance in the urine, suggests that the membrane through which the bacteria pass, has been modified by the action of toxin. Biedl and Kraus, on the other hand, after making cultivations of the urine as it passed from the ureters, came to the conclusion that "micro-organisms circulating in the blood can be excreted through the completely intact kidney by its physiological action." They found, after intra-venous injection of 3–5 c.c. of a broth culture of *Staph. pyogenes aureus*, that the micro-organisms appeared in the urine after the lapse of from twelve to seventy-five minutes in dogs, much earlier in rabbits. They base their conclusions on the normality of the urine in other respects, on the normal macroscopic and microscopic appearance of the kidney, on the fact that excretion of micro-organisms in these cases varies in rate from time to time, but is furthered by intra-venous injection of a diuretic (glucose), and on the assumption that, in many cases, so short a time (five minutes) elapsed between introduction of micro-organisms into the blood and their escape by the kidney, that destructive action of toxins and fever may be excluded. Other evidence is just as conflicting, but as in the analogous case of passage of bacteria from mother to fœtus through the placenta, most authorities are inclined to believe that an actual injury of the blood-vessels has been produced though it may not have amounted to rupture.

Klein found diphtheria bacilli in the milk of cows that had been inoculated with diphtheria bacilli over the shoulder. Their appearance in the milk was preceded by the formation of vesicles and ulcers on the udder. Abbott was unable to confirm Klein, but this is attributed by Klein to the fact that Abbott used cultures of insufficient virulence. Brunner found after injection of *B. anthracis* or *B. prodigiosus* into the blood that if he stimulated the nerves, these micro-organisms were excreted by the sweat.

Some poisons are excreted by special paths: to this point passing allusion has already been made. Thus, pilocarpine is excreted with the sweat, phosphorus and toluylenediamin with the bile, mercury (perhaps) by the glands of the large intestine, carbolic acid and its allies with the urine, iodine with the urine, saliva, and bronchial secretions, bile-salts with the urine and (perhaps) with the saliva.

Reference has already been made to the importance of putrefactive changes occurring in the urine while still within the body. Morbid conditions dependent upon this cause obviously come into the present section.

When urine is allowed to stand, it becomes cloudy from the growth in it of various micro-organisms, the most important of which, from our point of view, is *Micrococcus ureæ*, a micro-organism which has the specific property of leading to the hydration of urea and its conversion into ammonium carbonate. With this change the urine becomes "ammoniacal," and gives off gaseous ammonia; at the same time, of course, its reaction changes from acid to alkaline. Conditions such as warmth, presence of albumin or mucus, etc., favour growth of this micro-organism as they do growth of most other micro-organisms.

The altered reaction of the urine leads to the deposition of calcium phosphate, since phosphates are insoluble in alkaline fluids. In these cases the calcium phosphate is always precipitated in an amorphous form, and it constitutes a part of the white crust that is seen upon calculi and other objects when they have remained for some time in a bladder which is the seat of cystitis, and which contains ammoniacal urine. The presence of ammonium carbonate in urine, along with magnesium phosphate, leads to the deposition of characteristic crystals of ammonio-magnesium phosphate.

VII. **Morbid Conditions of known or suspected dependence upon Alterations in Internal Secretions.**—We have already discussed certain conditions which might with justice be considered under this heading (diabetes, uræmia), but in them there was some modification of urine so marked as to attract especial attention. In the present class we shall have to consider morbid conditions in which urine, fæces, etc., are practically unaltered, and in which the changes induced by alteration of the internal secretion are manifested in other ways. The "glands" with which we are here concerned are (i.) the thyroid body, (ii.) the supra-renal bodies, (iii.) the pituitary body, all of which agree in the fact that they are "ductless," and possess no external secretion; in addition, a word must be said concerning (iv.) the sex-glands.

(i.) **The Thyroid Body.**—It is now fully recognised that the thyroid body possesses an internal secretion, and that the morbid conditions known as "cretinism" and "myxœdema" depend upon atrophy of the thyroid and absence of its secretion. On the other hand—though there is not unanimity upon this point—many authorities believe that the symptoms of exophthalmic goître, a disease in which the thyroid body is enlarged, are due to an excessive formation of the special internal secretion.

(*a*) *Cretinism and Myxœdema.*—Cretinism is a mental and physical deformity associated with alteration of the thyroid body, which occurs in children of goîtrous parents, and which is therefore principally seen in regions where goître is endemic. In goître, as in cretinism, the thyroid body is diseased, for in both conditions it is either fibrotic or cystic or both. But whereas in goître the gland is always enlarged, and often to an enormous extent, in cretinism, though it may indeed be enlarged, this is rarely the case, but in most cretins the gland is either atrophied or unaltered in size. Cretinism does not especially affect either sex; it is a congenital condition, or, at all events, it manifests itself at a very early age. In myxœdema we have a cretinoid condition, though it is not apparently connected in any way with goître in the parents. The disease usually affects adult women, but men are not exempt. The myxœdematous patient is "unwieldy in mind and in body." Her features are changed, becoming broad, flattened, and expressionless, the alæ nasi and lips are thickened, speech is slow, and articulation (partly from increase in size of the tongue and lips) is bad; the hands become broad and spade-like, the mental condition changes to one of placid indifference;[1] the skin over the whole body, but especially that of the face, becomes loose, flabby, coarse, and appears œdematous; the hair falls out; temperature is sub-normal, and the patient complains of chilliness.

We shall not discuss the pathology of cretinism separately, for more work has been done upon the subject of myxœdema, and probably the pathology of the two conditions is closely alike.

Present views as to the pathology of myxœdema really date from 1856, when Schiff pointed out that complete removal of the thyroid body in dogs is generally fatal. But it was not until 1873 that Gull drew attention to and described myxœdema; in 1878 Ord reconsidered and added to our clinical knowledge of the subject; in 1882–83 Reverdin pointed out that cachectic symptoms of a certain kind frequently occur in man after removal of the thyroid for goître; in 1883 Kocher published notes of 104 cases of goître on which he had operated: in twenty-four the gland was completely removed, and in eighteen of these the patient showed symptoms similar to those described by Reverdin, viz., weakness, coldness, pains in the arms and legs, thickening of the skin, falling out of hair, weakened intelligence, lacrymosity, slowness of speech—in a word, myxœdema; in 1885 Horsley produced myxœdema in monkeys by removal of the thyroid body; in 1891 Murray showed the beneficial effects in myxœdema of subcutaneous injection of thyroid extract.

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[1] According to Clouston, mental symptoms in myxœdema are very varied. As a rule, there is general loss of memory, diminution in attention, and diminution in emotion, though the patient is often lacrymose. There is never complete dementia, but patients may become melancholic with visual and aural hallucinations, illusions, and, especially, suspicions; frequently there are maniacal outbreaks. Some, but not all, of the cases improve under treatment with thyroid extract.

All animals do not react to removal of the thyroid body in the same way. This is clearly shown by Horsley's experiments, for while in monkeys, and exceptionally in cats, he obtained myxœdematous changes with slow onset, in dogs and in the majority of cats he obtained a rapid onset of pronounced symptoms indicating extreme irritation of the nervous and muscular systems (tremors, tetany, convulsions). The following description of the symptoms is given by Lorrain Smith, who worked principally with cats and dogs. He found that even in the same species of animal the symptoms vary considerably. As a rule, in the first stage there is muscular twitching, which occurs only when the animal is stimulated mechanically, or makes a voluntary effort; in the second stage twitchings occur spontaneously but intermittently; in the third stage the spasms become of larger size, they increase in severity until they resemble epileptiform convulsions, the animal becomes dull and sluggish, and in such a condition he dies. So long as the symptoms do not extend beyond muscular twitching, the animal survives for some time, though exacerbations occur and he progressively wastes, but when convulsions have set in the end is near.

Now, though in man removal of the thyroid body leads to myxœdematous symptoms, in some cases, as Mickulicz and von Eiselsberg have pointed out, total extirpation is followed by tetany, or even epileptiform convulsions. Experiments upon lower animals may therefore be justly applied to the elucidation of the pathology of myxœdema in man.

In order to produce the characteristic symptoms it is necessary to remove all thyroideal tissue, the thyroid body, the parathyroids, and any accessory thyroids that may be present; in many cases (dogs and rabbits) where symptoms are absent or ill-defined, the explanation is that parathyroids have not been removed with the gland, but have taken on its function after its extirpation. As in the case of the pancreas, subcutaneous grafting of thyroideal tissue prevents the onset of symptoms, or at least prolongs life. Subcutaneous injections of extracts made from thyroids of other animals, or even feeding with thyroids, often causes amelioration or even cure (Béclère) of myxœdema in man, but in lower animals this is not so clearly the case. In monkeys, injection of thyroid extract does not with certainty prevent the onset of specific symptoms after thyroidectomy, and in dogs, thyroid-feeding after thyroidectomy at most secures a brief prolongation of life. In this connection it may be mentioned that the good effects obtained by injection of thyroid extract and thyroid-feeding in myxœdematous patients led to great hopes that similar benefit would be obtained in diabetes by similar treatment with pancreas. These hopes have not been fulfilled, either in diabetic patients or in dogs rendered diabetic by removal of the pancreas.

It was at first thought that there is some relation between the thyroid and the spleen, but this has been contradicted (Tizzoni, de Quervain) and is probably not the case. On the other hand, there is evidence that a relationship exists between the thyroid and the pituitary bodies. Rogowicz found after extirpation of the thyroid in rabbits that the pituitary body increases in size, and his results have been confirmed by Stieda and by Gley. Gley also found that symptoms fail to appear or are trivial, and in particular convulsions are absent, if complete thyroidectomy is carried out by successive removal of portions of the gland, so that the pituitary body has time to hypertrophy. Boyce and Beadles, too, describe cases of myxœdema and sporadic cretinism in which hypertrophy of the pituitary body co-existed with atrophy of the thyroid; moreover, they point out that the hypertrophy of the pituitary body, which is so commonly seen in acromegaly, is often associated with alteration of the thyroid, whether that body be atrophied, hypertrophied, or cystic.

Reference has already been made to the fact determined by Lorrain Smith, that animals from which the thyroid body has been removed, when exposed to variations of external temperature, show that in them the mechanism presiding over heat-loss is deranged. We have here no doubt the explanation of the chilliness and sub-normal temperature of myxœdematous patients.

We must now consider the way in which removal of the thyroid produces its specific symptoms. Putting aside the view—early suggested but soon discarded—that the symptoms after thyroidectomy are due to injury of nerves, and in particular of the cervical sympathetic, two theories have been put forward to explain the facts. The first is that of "auto-toxication," according to which the symptoms are due to accumulation in the blood of substances which, under normal conditions, are destroyed by the thyroid body. The second is that of "internal secretion," according to which the symptoms are due to absence of a substance normally formed by the gland and thrown into the blood either directly or by way of the lymphatics. The latter view is the one at the present time generally adopted and it has the greater amount of evidence in its support.

Endeavours have been made to isolate the active principle of the thyroid internal secretion, and perhaps it lies in the iodine-containing substance ("thyroiodin") found by Baumann in the thyroids of sheep. Baumann found that if the thyroids of sheep be boiled for twenty-four hours with 10 per cent. sulphuric acid the active principle is not destroyed, and that the substance precipitated after cooling such a decoction contains nearly 10 per cent. of iodine. Hutchison corroborated these results, and showed further that the active principle and the iodine reside principally in the colloid substance. Dividing the colloid into proteid and non-proteid components, Hutchison finds that the iodine resides in both, but to a far greater extent in the non-proteid portion. It seems, therefore, that the active principle is in some way connected with iodine, and it is remarkable in this connection that of the thyroid extracts used therapeutically in myxœdema, those which have been found efficacious are exactly those which, containing colloid (Hutchison), contain iodine.

(*b*) *Exophthalmic Goître* (*Graves' Disease, Basedow's Disease*).—

Exophthalmic goître, as its name implies, is a disease characterised by protrusion of the eyeballs (exophthalmos) and goître; in addition there is marked tachycardia, the rate of heart-beat being sometimes 120 in the minute, or more. Mental symptoms are also present, and in some cases the disease ends with acute mania. As in every other disease the symptoms are not always the same: sometimes there is little goître, sometimes exophthalmos is absent or but little marked, sometimes the psychical symptoms are slight; but in most cases all of these are present, and it is very rare for the rate of heart-beat to be normal. Like myxœdema, the disease chiefly affects women, though women of fewer years; men, however, are not exempt.

The pathology of exophthalmic goître is by no means clear. At the present time the chief divergence of opinion is as to whether exophthalmic goître is primarily a disease of the thyroid body, or primarily a disease of the nervous system, of which the thyroid change is a result. In favour of the primarily nervous view are the facts that exophthalmic goître is greatly dependent upon mental emotions, especially fright, that it is associated with other psychical changes, that the symptoms may largely be explained by assuming an alteration of the vaso-motor centre, and that often fibrotic changes are found in the cervical sympathetic, a nerve which has close relations with the vaso-motor centre. A nervous explanation is adopted by many authors.

On the other hand, the primarily thyroid view is adopted by some authorities, partly because of its *a priori* probability, now that the importance of thyroid internal secretion has been shown in the case of myxœdema, and partly because removal of a portion of the gland causes an improvement or leads to cure of exophthalmic goître; according to Marie, this occurs in 80 per cent. of operated cases. Against this view is the fact that feeding with thyroid and injection with thyroid extract do not aggravate exophthalmic goître as this view would lead us to expect. Moreover, Sollier has shown that in rare cases myxœdema and exophthalmic goître may co-exist in the same patient, and of course it is impossible to assume, if the myxœdema is due to deficiency of thyroid internal secretion, that the exophthalmic goître depends upon hyper-secretion.

Nor even among the supporters of the two views set forward above is there accord. Some who hold to the nervous explanation look on the disease as independent of organic nerve lesion—in other words, as a neurosis. Others regard it as being dependent upon a definite lesion: thus Mannheim, from careful examination of severe and fatal cases, concludes that the disease is caused by organic changes in the medulla oblongata, and others have ascribed it to sclerosis of the sympathetic.

But whether the thyroid body is primarily or secondarily affected, at the present time the tendency is to regard the symptoms of exophthalmic goître as being produced by abnormal thyroid action, which leads to circulation in the blood of some toxic substance that affects the central nervous system, and particularly the vaso-motor centre. Nevertheless, there is difficulty in accepting even this view, for, as Edmunds points out, there is no evidence that thyroid secretion can produce exophthalmos, while there is evidence in the monkey (Sherrington) that it can be produced by stimulation of the cervical sympathetic.

Concisely put, there are at least five different views as to the pathology of exophthalmic goître:—

(1) The disease is a neurosis, exophthalmos, goître, cardiac symptoms all being dependent upon functional alteration of the vaso-motor centre, and independent of one another (Buschau).

(2) The disease is due to organic lesion of the nervous system, whether of the sympathetic, or of the brain, or of the cord (Mannheim).

(3) The disease is primarily due to hypertrophy of the thyroid body and excessive formation of a normal, or formation of an abnormal, internal secretion; this secretion acts upon the central nervous system, and especially upon the vaso-motor centre.

(4) The disease is primarily one of the central nervous system, secondarily one of the thyroid, and tertiarily one of the central nervous system owing to the effect upon an abnormal nervous system of an abnormal thyroid secretion.

(5) The disease is primarily one of the blood, secondarily one of the thyroid, tertiarily one of the central nervous system (Eulenberg).

In a word, no fully satisfactory pathology for exophthalmic goître can at the present time be given.

(ii.) **The Supra-renal (Adrenal) Bodies.**[1]—In connection with the adrenal bodies we have to consider the disease first described by Addison in 1855, and known by his name. Addison's disease is characterised by severe and progressive muscular weakness with anæmia, by cardiac feebleness and a tendency to syncope, by nausea with retching and vomiting, and in many cases, though not in all, by a peculiar pigmentation ("bronzing") of the skin in exposed parts and parts liable to pressure. It was pointed out by Addison, and is fully allowed, that this condition is associated with disease of the adrenals.

We may put on one side the earlier work in which the adrenals were extirpated, for the results were conflicting, though in most cases, death rapidly followed the operation. Brown-Séquard, however, in 1856, extirpated one or both adrenals, and noted that the animals, in the few hours elapsing before their death, showed muscular and cardiac weakness, coma, and convulsions; but these symptoms might readily follow any severe operation, especially if accompanied by much loss of blood, so they are not conclusive. In 1889 Tizzoni published a long series of experiments showing that in rabbits and dogs destruction of the adrenals leads to death sooner or later, but that if death is delayed for some time, it is preceded by a definite train of symptoms, which in many points (pigmentation, progressive weakness, wasting, nervous symptoms, etc.) bear a marked resemblance to those of Addison's disease. After death he found alterations in the cerebrum and cerebellum, spinal cord, peripheral nerves, and pia mater, which were always more marked in the grey matter, and which consisted in hæmorrhages, migration of leucocytes, alteration of vessel walls, congestion and interference with lymph-circulation. He therefore concluded that "the supra-renals are, in any case, to be regarded as organs which are closely bound up with the nervous system, and this view is confirmed by the clinical appearances."

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[1] An exhaustive account of our knowledge concerning the adrenal bodies was given by Rolleston in his *Goulstonian Lectures* (reported in *Brit. Med. Journ.*, 1895, vol. i.).

The view that there is a close connection between the adrenals and the central nervous system is old; Frey (1849), Kölliker (1854), Luschka (1863), all agreed upon the point, and Rayer (1883) drew attention to the fact, which has received plentiful confirmation, that in acephalic monsters the adrenals are completely wanting or are badly developed, whereas in infancy these organs are normally of relatively large size. Relying on observations such as these, some authors hold that Addison's disease is due to central nervous lesions (functional or organic) secondarily induced by the adrenal changes, through the medium of the abdominal sympathetic nerves and ganglia with which these bodies are in close anatomical connection. Even the pigmentation has been regarded as dependent upon nervous influences, as it certainly is in many of the lower animals. Thus Raymond cites Milne Edwards and Bert (chameleon), Pouchet and Vulpian (frog) as having shown that cells charged with the elaboration of pigment are definitely under the influence of the nervous system, and Gaule, Canini, Ehrmann and Lode as having actually observed the termination of nerves in chromatoblasts. Raymond himself considers that the pigmentation of Addison's disease results "from a reflex act producing trophic change"; in other words, that it is one manifestation of a series of trophic changes initiated in the body by the condition of the adrenal bodies through the medium of the central nervous system.

But when the existence of internal secretions was recognised, and when the relationship between the thyroid body and myxœdema, the pancreas and diabetes, was shown, a tendency arose to seek an explanation of Addison's disease in a change of the blood induced by the absence, or rather the disorganisation, of the adrenals. Here, too, as in the case of myxœdema, opinions differ as to whether the condition depends upon auto-toxication or upon absence of a normal internal secretion.

Abelous and Langlois found when animals, deprived of their adrenals, are caused to perform muscular work, that toxic symptoms readily arise, and they conclude that the function of the adrenals is to destroy the toxic products of muscular and nervous work. They found, moreover, that the blood of animals from which the adrenals have been removed, and which have been fatigued, is more toxic than the blood of animals which have been similarly fatigued, but from which the adrenals have not been removed. These results have been confirmed by Albanese and by Dubois. Dubois found in addition that the toxicity of an extract of adrenal body is greater if the animal, before removal of the organ, has been caused to undergo muscular exertion. From these experiments it has been argued that Addison's disease is an auto-toxication.

But there is no doubt that an organic substance of doubtful composition, but possessed of powerful physiological action, can be extracted from the adrenal bodies. Oliver and Schäfer obtained from the medullary portion, and from that alone, a substance which acts on muscular tissue generally, but especially on the heart and blood-vessels. Intra-venous injection of as small a quantity as one-millionth of the weight of the dried gland leads to an enormous though transient rise of blood-pressure. When the vagi are intact, the extract, acting through the cardio-inhibitory centre, slows the heart; but when the vagi are cut, it accelerates the heart by direct action. The meaning of this difference is obscure. The substance was supposed by Szymonowicz and Cybulski to act by way of the vaso-motor centre; but Oliver and Schäfer have shown, by the plethysmographic and other methods after section of the spinal cord, and Gottlieb has shown, by injecting the extract into animals under the deepest chloral narcosis (in which the vaso-motor centre is paralysed), that the substance acts directly upon the involuntary muscle of the blood-vessels. Gottlieb further found that the substance raises the activity of the heart, for if, by continued doses of chloral, the heart is affected to so great an extent that it ceases to contract, subsequent injection of extract of supra-renal, if aided by slight compression of the thorax, is able to restore spontaneous cardiac activity, even though it have been in abeyance for one minute. Oliver and Schäfer conclude that the adrenals elaborate and throw into the blood a substance[1] which assists in keeping up vascular tone. Whether this be so or no, there is no doubt that the adrenals form an internal secretion, and that absence of a substance having properties such as those described as belonging to supra-renal extract, might well account for many of the symptoms of Addison's disease.

But though the adrenal bodies have an internal secretion, as these experiments prove beyond doubt, it is not certain that this is their only function. The experiments upon which those authors rely who maintain the auto-toxication view, seem very definite, so that even if we discard the older view, which regards the adrenals as intimately connected with the central nervous system, it is not clear whether we must consider Addison's disease as dependent upon auto-toxication or upon absence of adrenal internal secretion. It is by no means certain, however, that we are justified in entirely discarding a belief in the close connection of adrenals with the central nervous system. For it is in the highest degree significant that where the adrenals are absent or insufficiently developed, there is almost always incomplete formation or defect of the brain, that in anencephalia the adrenals are completely wanting or badly developed, and that the only regions in the body where lecithin is constantly present in large amounts, are the brain and adrenal bodies.[2] Further experiment is necessary before we can determine which of these views, if any of them, is correct.

(iii.) **The Pituitary Body.**—In connection with the pituitary body we have to consider the disease described by Marie and

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[1] The view that the adrenals take something from the blood, elaborate it, and return it to the blood, is not new. It was put forward by Nagel in 1836 and Ecker in 1846, and though neither the existence of Addison's disease, nor its connection with the adrenals, had at that time been suspected, the view taken by these earlier writers was essentially that these organs normally produce what we now speak of as "an internal secretion."

[2] Those who wish to pursue further the subject of the relationship of the adrenals to the nervous system and the pathology of Addison's disease, should read a paper by Alexander (*Ziegler's Beitr.*, vol. xi. p. 142, 1892), which gives a good summary of our knowledge on the subject.

Souza-Leite in 1885 under the name of acromegaly. Acromegaly is chiefly characterised by an increase in size of the bones of the hands, feet, and face. In the face the lower jaw is principally affected, with the result that the face becomes elongated and ponderous. The lips become thick, the skin hypertrophied, the hair coarse, but the general appearance of the patient is different from that in myxœdema, though mistakes in diagnosis have been made. The patient almost always complains of headache, he perspires profusely, is lethargic, and speaks thickly. Sometimes he becomes blind, but intelligence and memory are, as a rule, not seriously affected.

Though not many cases have been described, it has been found that in acromegalous patients the pituitary body is always altered, being either hypertrophied, the seat of new-growth, or atrophied and cystic.

As to the relation between the pituitary change and acromegaly little can be said. The suggestion has been made that the disease depends upon some alteration of a pituitary internal secretion, but evidence for this is very slight. Nevertheless, the pituitary body apparently has an internal secretion. Oliver and Schäfer have found that extract of pituitary body, when injected into animals, produces symptoms having a general resemblance to those produced by injection of supra-renal extract. It causes a great rise of blood-pressure, which, however, is produced more slowly, is longer maintained, and requires injection of larger doses to produce the same result than is the case after injection of supra-renal extract. However, they find that the rise of blood-pressure caused by injection of pituitary extract, like that caused by injection of supra-renal extract, is due to direct action of the active principle on the muscular walls of the arterioles. It must be mentioned, however, that Mairet and Bosc, using the pituitary body of the ox, found that it produces very slight effects, whether on rabbits, dogs, or man, and whether given by subcutaneous injection of an extract or by feeding.

We have already referred to changes in the pituitary body occurring along with myxœdema and experimental removal of the thyroid body (p. 684). It is only necessary here to add that in acromegaly the thyroid body is often found to be the seat of change (hypertrophy, atrophy, cysts). Whether these two organs are accessory to one another, it is impossible to say with certainty, but it does not seem improbable, from the evidence before us, that this is the case. Nevertheless, Oliver and Schäfer pronounce against this view, because they find that thyroid extract and pituitary extract have diametrically opposite physiological actions.

(iv.) **The Sex-glands.**—Upon this subject not much need be said, but the sex-glands must not be passed over in silence.

It is well known how profound a change may be produced on the body generally by removal of testes or ovaries. The eunuch, with his beardless face, his small larynx and shrill voice, his enormous deposit of fat over the abdomen, his alteration of character, shows in man the effects of removal of the testes in childhood. The differences in character, strength, and size between the stallion and gelding, the bull and ox, the ram and wether, the cock and capon, the castrated and the normal domestic cat, are all evidences in the same direction. In women, the alteration of character, the growth of hair on the chin and upper lip that often supervene at the climacteric, the masculinity of appearance and of character that often follows ovariotomy, or is seen in women with deficient development of the sex-organs, show the importance of the ovaries to the female economy. So, too, the marvellous change in appearance that sometimes occurs in the hen golden pheasant (and other hen birds), when, after a moult, she adopts the plumage of the cock bird, and even his note, is always associated with an atrophic or otherwise diseased condition of the ovaries (*cf.* Bland Sutton).

Phenomena of this nature are unmistakable enough, but the way in which the glands exercise their normal influence is obscure. It is not known whether they act reflexly on the nervous system or by virtue of an internal secretion. Brown-Séquard, to whom, above all, we owe the doctrine of internal secretions, held the latter view, and asserted that in himself and in others he had observed the greatest benefit in old age and other senile conditions from injection of testicular extract. But it is difficult in these cases to exclude the possibility that the benefit derived was due to auto-suggestion or suggestion. And yet it does not seem unreasonable, now that we have learned the importance of the pancreas, the thyroid, the adrenals, and possibly the pituitary body and the kidneys, to expect that the sex-glands also possess an internal secretion; the more so since we have ample evidence that absence of these organs leads to profound changes of mind and body.

Other organs such as spleen (*cf.* Laudenbach) and salivary glands (Oliver and Schäfer) have been removed experimentally without the sequence of any ill effects attributable to their absence. It cannot, however, be argued from these experiments that the organs in question do not possess an internal secretion, for many other tissues are present in the body which can, more or less fully, take on their functions in their absence. It can, however, be said that the salivary glands and spleen do not possess *specific* internal secretions.

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# CHAPTER XIV.

## The Pathology of Respiration.

*Synopsis.*

- I. Effects of Changes in the Air-Passages.
  - (i) The Mouth, Nose, and Pharynx.
  - (ii) The Larynx and Trachea.
    - Coughing and Sneezing, and their Pathological Effects.
  - (iii) The Bronchi.
    - (*a*) Bronchitis.
    - (*b*) Asthma.
  - (iv) The Pulmonary Alveoli.
    - (*a*) Emphysema.
    - (*b*) Obliteration of Alveolar Cavity from within.
    - (*c*) Collapse of Lung.
  - (v) The Pleuræ and Pleural Cavities.
    - A. The Pleuræ.
    - B. The Pleural Cavities.
      - (1) Pleural Effusion.
      - (2) Pneumothorax.
      - (3) Absorption from Pleural Cavity.
- II. Effects of Changes in Respiratory Movements.
  - (i) Changes in Skeleton.
- II. Effects of Changes in Respiratory Movements.
  - (ii) Changes in Musculature.
- III. Effects of Circulatory Disorders.
  - (i) Cardiac Dyspnœa.
  - (ii) Renal Dyspnœa.
  - (iii) Heat Dyspnœa.
- IV. Effects of Morbid Conditions of the Blood.
- V. Effects of Abnormality of the Respired Air.
  - (i) Deficiency of Oxygen.
    - (*a*) Mountain Sickness.
    - (*b*) Poisoning with Carbon Monoxide.
  - (ii) Increase of Carbon Dioxide.
  - (iii) Presence of Abnormal Gaseous Constituents.
    - Inhalation of Chloroform and Ether.
- VI. Asphyxia, Dyspnœa, and Orthopnœa.
- VII. Cheyne-Stokes Respiration.

The pathology of respiration is extremely complicated, for respiration is partly involuntary, partly voluntary, and is not only assimilative like the digestive process, but also excretory like the renal function. It is a process whereby the blood gains oxygen, and loses carbonic acid and water; it is a powerful factor in connection with the circulation,—now an assistance, now a hindrance; it is one of the most important means of heat regulation. And just as the blood and heart, and, through them, the nervous system and nutrition generally, are dependent upon respiration, so respiration in its turn is dependent upon each and all of them. Hence the causes of disordered respiration and its effects are widespread.

Modifications of respiration are almost always attempts, whether successful or not, at restoring an equilibrium. In most cases they aim at restoring a normal degree of gas-exchange, but sometimes at restoring the normal body temperature.

The actual means whereby this equilibrium is brought about, and the particular form of altered respiration adopted, vary considerably in different cases, for the means whereby the same end can be attained are manifold. This is equally true in health and in disease. The healthy man undergoing bodily exercise increases his respiration in order to restore the balance between thermogenesis and thermolysis. If his abdominal muscles are unrestrained, he breathes very largely by the diaphragm; but if descent of the diaphragm is restrained, the costal muscles take up its work and carry it out. The typhoid patient increases his respiration also, and, in part, for the same object; but whereas with the initial rise of temperature, when his respiratory muscles are comparatively normal, his respiration is slightly increased in rate and considerably deepened, as the disease goes on, and his respiratory muscles become enfeebled, the rate of respiration increases still further, but the depth of individual respirations diminishes.

Abnormalities of respiration may concern rate or depth of complete respirations, the relative durations of inspiration and expiration, or respiratory rhythm. Though we shall have to consider all of these conditions, it would not be convenient to discuss the pathology of respiration under these headings. A more convenient course is to consider them, as far as possible, according to the factor which is primarily responsible for their occurrence. Since, therefore, normal respiration is dependent upon the condition of (1) the lungs and air-passages, (2) the respiratory movements, (3) the heart and circulation, (4) the blood, and (5) the characters of the air breathed, we shall consider the effects of changes in these factors upon respiration.

**I. Effects of Changes in the Air-Passages upon Respiration.**—(i.) **The Mouth, Nose, and Pharynx.**—Owing to the fact that air can reach the pharynx by either nostril, or by the mouth, in sufficient quantity for normal respiration, morbid conditions of the mouth and nose are of relatively small importance in the pathology of respiration. It is true that when the posterior nares are blocked by adenoid growths, or when similar conditions involving the nose obtain, the breathing assumes special characters, being carried on solely by the mouth, and in particular being accompanied by "nasal" phonation and by snoring at night. But these respiratory modifications, though of much diagnostic significance, are, as a rule, unimportant pathologically. Nevertheless, the fact that in cases of this description, air can only enter by the mouth, may become of extreme importance from an alimentary point of view. This is especially the case where it is necessary that food should be taken often, as, for example, in infants and sick persons. Then, the constant opening of the mouth necessary for respiration may be very serious, and in the case of infants at the breast, it may lead to severe mal-nutrition and exhaustion from want of food.

Pharyngeal conditions only lead to disorders of respiration by way of stenosis, and then the obstructing body must be very large, owing to the large size of the pharynx. Apart from accidental lodgment of such substances as masses of food, etc., the important causes of pharyngeal stenosis are bilateral enlargement of the tonsils, quinsy, and aneurysm of the internal carotid. The modification in respiration produced by such causes as these, is identical with that which occurs with stenosis of the larynx or trachea, and therefore will not be separately discussed.

Secondarily, morbid conditions of the mouth, nose, and pharynx may be of importance in the pathology of respiration, by leading to pulmonary disease; but, as a rule, this only occurs when for some reason the sensibility of the larynx or trachea has been lowered or abolished (as, for example, during administration of anæsthetics), or when laryngeal muscles are paralysed. Under either of these conditions the cough-reflex is defective.

(ii.) **The Larynx and Trachea.**—At the larynx the air-passages begin to have a great importance in the pathology of respiration. For not only is there no alternative path for the respired air, but also the glottis itself is the narrowest point between the lips and the bifurcation of the trachea. Associated with this fact is the fact that the glottis is exquisitely sensitive, and that from it, coughing, as a reflex act, may be more readily set up than from any other part of the whole respiratory tract, though the mucous membrane of the trachea and bronchi are highly sensitive also. The act of coughing is so important, both for good and for ill, in the pathology of respiration, that it must at once receive special attention. At the same time, sneezing may also be considered.

*Coughing and Sneezing.*—Coughing and sneezing are essentially defensive mechanisms, and are no doubt primarily directed towards the removal of any substance which irritates the mucous membrane of the respiratory tract. Both are reflex acts, but coughing may be carried out voluntarily.

Sneezing occurs when the mucous membrane of the nose is the seat of irritation, the afferent fibres especially concerned in the act being those of the olfactory branch of the fifth nerve. Nevertheless, sneezing may be induced by impulses which apparently pass upwards by other nerves, for many persons sneeze on coming suddenly into a bright light, or on exposure of the body to cold. The act of sneezing consists in a deep inspiration, followed by a violent expiration in which a blast of air passes out principally by the nose, but in part also through the half-closed mouth.

Coughing, as a reflex act, is most readily induced by stimulation of the larynx, the under surface of the epiglottis and the parts in the neighbourhood, the trachea, or the bronchi. When the offending substance is in the neighbourhood of the larynx, the afferent nerve concerned in the act is the superior laryngeal. The act may be induced reflexly by stimulation of afferent nerves other than those of the respiratory tract. Thus it often occurs along with irritation of the external auditory meatus, where the afferent nerve is perhaps the auricular branch of the vagus, and on exposure of the body to cold.[1] The act of coughing consists in taking a deep inspiration, then closing the glottis, and, when the intra-thoracic pressure has been considerably raised by an effort of forcible expiration, opening the glottis suddenly; the pent-up air rushes forth with sufficient violence to set the vocal cords vibrating.

The readiness with which sneezing and coughing are called forth by an offending substance varies much. Thus, on the one hand, the nasal mucous membrane of the confirmed snuff-taker in course of time suffers a great diminution of sensibility, and such a person rarely sneezes when he "takes snuff." So in chronic inflammatory conditions—*e.g.*, chronic bronchitis—where the products of inflammation are more or less constantly in contact with the bronchial walls, sensibility becomes dulled, and cough only occurs when the offending substance has collected in relatively large quantities. On the other hand, in acute inflammatory conditions, both of nose and of laryngeal or tracheal mucous membranes, the hyperæmia induces hyper-sensitiveness, and helps to account for the constant sneezing of a commencing catarrh, the constant cough of laryngitis.

*Pathological Effects of Coughing.*—The effects of sneezing and coughing are beneficial, in so far as they expel irritating substances from the respiratory tract. But, not to mention the general distress and the loss of sleep that are produced by incessant cough, the increase of intra-thoracic pressure, which is an essential factor in coughing, often leads, if cough be persistent, to serious results. These may concern either lungs or blood-vessels, owing to the fact that variations of intra-thoracic pressure bear upon the lungs and the heart with the great blood-vessels attached to it. Normally, the intra-thoracic pressure is, of course, negative. In the dead body, the pressure is about 8 mm. Hg below that of the atmosphere; and this may be taken as the pressure obtaining at the end of an ordinary expiration. With inspiration, the mean negative pressure is increased, becoming in man at the end of a deep inspiration equal to about 30 mm. of Hg (Stewart). In ordinary expiration, muscular activity plays no part, but the act is simply due to a recoil of the thoracic walls from the position into which they have been brought by the contraction of inspiratory muscles, especially the diaphragm. In forced expiration, the intra-thoracic pressure still further approximates towards that of the atmosphere, and may at times actually become positive. This is especially liable to be the case in coughing.

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[1] We know very little concerning the cough and sneezing reflexes, but it does not seem to me that it is absolutely necessary to accept the statement commonly made, and which I have followed in the text, that many different nerves may carry up the afferent impulses. Exposure of the body to cold air implies stimulation of the nasal and laryngeal mucous membranes by cold air, and irritation of the external auditory meatus leads to a "tickling in the throat," as anyone can determine for himself. With regard to sneezing on exposure to a bright light, it is quite possible that the light only acts indirectly, by causing a secretion of tears which pass into the nose by the lacrymal duct, and stimulate the nasal mucous membrane.

*Circulatory Changes.*—As regards the circulation, even the variations of intra-thoracic pressure coincident with normal respiration have important results. The mean negative pressure obtaining within the thorax tends to draw the blood from parts outside the thorax into the heart. Owing to the disposition of valves and the relative thinness of the walls of veins, this force especially concerns the venous blood-flow. Hence inspiration favours filling of the heart, increases the velocity of the blood-flow (but diminishes the pressure) in the great veins, increases the rate and the force of heart-beat, quickens the pulse and makes it more forcible, increases the amount of blood thrown out by the left ventricle at each systole, and raises the blood-pressure. Expiration has the opposite effects; in particular, it raises the venous blood-pressure.

When expiration is forcible and the intra-thoracic pressure becomes positive, as it does in violent coughing, the obstruction to venous blood-flow at the entrance of the veins into the thorax becomes plainly evident by the swelling of cervical and facial veins, and the congestion and blueness of the skin, which occur. But the increase of venous pressure acts back upon the small veins and capillaries, and if they are unable to withstand the sudden stress, they rupture. This is the explanation of the epistaxis and the conjunctival ecchymoses often seen in children suffering from whooping-cough. The explanation of such hæmorrhage as occurs in cerebral apoplexy, and is often brought about by a violent expiratory effort, such as cough or straining at stool, is somewhat different. Here arterioles are concerned, and the explanation lies in the facts that the vessel walls are already the seats of disease, and that the violent expiratory effort with closed glottis raises the arterial blood-pressure instead of lowering it, as is the case in normal, effortless expiration. Rupture of healthy arterioles is never caused by even the most forcible expiratory effort. The rise of arterial blood-pressure in cough and similar violent expiratory efforts is probably due to the increase of peripheral resistance and the increased force of heart-beat caused by contraction of many muscles, especially those of the abdominal wall.

*Pulmonary Changes* (*Emphysema*).—In the case of the lungs themselves, we must consider the constitution of the thoracic walls a little more closely. The thorax is indeed "a closed box," but it is one of which the walls are not of a uniform rigidity throughout. The ribs are highly resistant, the costal cartilages less so, at the costal interspaces there is neither bone nor cartilage, and at the root of the neck the thoracic wall is formed by little more than skin and subcutaneous tissue. Hence the effects of variations in intra-thoracic pressure are different at different regions of the thorax; when the intra-thoracic pressure is reduced the soft parts sink in, when it is increased they bulge. With the normal variations in pressure accompanying respiration, neither of these conditions is important, but when these variations become abnormal, the case is different.

Now, the rise of intra-thoracic pressure caused by violent expiratory efforts, such as cough (and we may add here the playing of wind instruments), is intra-pulmonary, and therefore the lungs will be most affected by the pressure within them at those points where they are least supported, in particular at the apices. A very clear demonstration of this fact, and of the consequences to which it leads in the lung, is given by the following simple experiment.

If a deflated india-rubber ball be held in the half-closed hand, and the pressure within the ball be raised considerably by forcing air into it, while at the same time the hand itself is held rigid, the india-rubber ball will bulge and become thinned at the points which are not supported by the fingers. The same is true of the lungs: they bulge at the apices, as anyone can readily determine for himself by placing the fingers in the supra-clavicular fossæ and making forcible expiration with a closed glottis. At the same time, the alveolar walls in these regions become distended and stretched. If this condition is frequently caused, and if, in particular, the elasticity of the lung has become impaired owing to disease, or is congenitally less than normal, the unsupported parts do not fully return to their normal size and shape with disappearance of the excessive intra-pulmonary pressure. They are left larger than normal, and since the strain to which they have been subjected frequently causes rupture of the alveolar walls, contiguous alveoli become converted into single large spaces, and form the bullæ which are so characteristic of pulmonary emphysema.

Here, then, we have an important result of persistent cough. Pulmonary emphysema is at the present time regarded as the effect of violent expiratory efforts upon a lung, the elasticity of which is impaired.[1] It is only necessary to add here that emphysema is almost invariably found along with chronic bronchitis, a disease in which the two factors, cough and impairment of lung tissue, are markedly present.

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[1] The modern explanation of the pathology of emphysema was first advanced in this country by Sir W. Jenner in 1856, but it had, in 1845, already been put forward in Germany by Mendelssohn. Two other theories, which are now of historical interest only, were put forward by Laennec, who first adequately described the condition, and by Gairdner of Edinburgh. Laennec's view was that the bronchi in bronchial catarrh being obstructed by swelling or by accumulation of mucus, the smaller expiratory force was unable to expel air that entered the alveoli during inspiration. Gairdner's view was that emphysema arises solely during inspiration, and that for its occurrence some part of the lung must have previously been rendered functionless by collapse, tubercle, or other cause. Under these conditions, enlargement of the thorax during inspiration must lead to undue expansion of the remaining alveoli. He therefore regarded emphysema as "compensatory." Sir R. Douglas Powell holds that the inherent elasticity of the thoracic cage, which normally tends to enlarge the thoracic cavity, is an important factor in the production of early stages of emphysema.

We must now return to consideration of changes in the larynx and trachea in connection with disordered respiration.

Apart from the cough by which they are accompanied, laryngeal and tracheal morbid conditions are important in the pathology of respiration in two ways: either (1) because they cause stenosis, or (2) because they permit foreign substances to gain access to the lungs.

(1) The most important causes of stenosis of the larynx and trachea, besides lodgment of foreign bodies, are laryngeal diphtheria, paralysis of the laryngeal abductor muscles, œdema of the glottis, laryngismus stridulus, cicatrices, cancer and other new-growths (whether affecting the air-tube itself, the thyroid body, the cervical glands, the œsophagus or other neighbouring part), aneurysm of the innominate or carotid arteries, whether acting by direct pressure or (as in the case of aortic aneurysm) by leading to paralysis of a posterior crico-arytenoid muscle by pressure on its nerve.

Under any of these conditions the entrance and exit of air to the lungs is impeded, and the extent to which this is the case varies according to the degree of stenosis. The impediment may be so slight as to pass unnoticed; it may be so great as rapidly to lead to death from asphyxia. Between these extremes every conceivable condition may be met with. In a well-marked case of obstruction the rate of respiration is considerably reduced, respiration itself is laboured, and the extraordinary muscles of inspiration and expiration are called into play. The duration of expiration is now equal to that of inspiration instead of being slightly greater, as is normally the case; but the actual duration of both phases of respiration is prolonged, and the comparative pause which in ordinary breathing obtains between an expiration and the following inspiration, is done away with. At the same time, the absence of sound which characterises normal, quiet breathing is exchanged for a more or less harsh, whistling noise (stridor) formed by passage of air over the seat of obstruction, and the soft rustling heard on auscultating the normal chest, with inspiration, gives place to a rough, to-and-fro, grating noise. The difficulty with which air enters and leaves the lungs is further shown by the recession of the soft parts in the supra-clavicular fossæ, the intercostal spaces, and the hypochondria and epigastrium that occurs along with inspiration, and the bulging of these parts that occurs with expiration. Lastly, a more or less well-marked cyanosis testifies to the deficient aëration of the blood, and a profuse perspiration to the muscular labour which the patient is undergoing; possibly, however, the sweating may, in part, be reflex, and depend upon the action of venous blood upon a medullary centre.

(2) The other way in which morbid conditions of the larynx and trachea may lead to disordered respiration, viz., by allowing access of foreign bodies to the lungs, is of equal importance. The chief cause of this accident is abolition of the cough-reflex, whether owing to insensitiveness of the laryngeal and tracheal mucous membrane, as in coma, or in anæsthesia induced by chloroform, ether, etc., or owing to paralysis of the laryngeal muscles (recurrent nerve paralysis) whereby that closure of the glottis, which is necessary to coughing, cannot be carried out. Under either of these circumstances, not only is the cough-reflex deficient, but also the rima glottidis lies open. Other conditions often assist in allowing foreign substances to pass the glottis and enter the bronchi or lungs. Thus in labio-glosso-laryngeal (bulbar) paralysis, the defective power of moulding a bolus of food, and directing the passage of solids and liquids from the mouth to the œsophagus, often leads to an accumulation in the pharynx or about the epiglottis, and allows portions to be inspired into the lungs. So also, in general paralysis of the insane, overfilling the mouth with food, combined with defective power of swallowing, frequently leads to the same result. Moreover, in paralytic conditions such as those which have been mentioned, the epiglottis remains in a motionless upright position, and does not afford a normal protection to the larynx.

Destruction of the epiglottis itself by ulceration (*e.g.*, syphilitic), apart from paralysis of pharyngeal and laryngeal muscles, is apparently not of the same importance in allowing foreign bodies to pass the glottis. The condition is fairly common among patients who have suffered severely from throat affection in syphilis, but septic pneumonia from inspiration of solids or liquids in these cases is much less frequent than might be expected. The epiglottis seems to be an inner line of defence for the glottis, and when the tongue and pharyngeal muscles act normally, its protection is not requisitioned. For, normally, by contraction of the muscles concerned in deglutition, the mass of solid or liquid is quickly thrown across the vertical line which passes through the rima glottidis, and crosses it at a considerable distance above the laryngeal opening itself. Hence, when the mass reaches the level of the glottis, it is already on a posterior plane, for it has been travelling down the posterior wall of the pharynx. But when the muscles of deglutition are weakened or paralysed, this is not the case, for then all the movements of the mass are slower, and the path which it follows, instead of approximating in shape to a right angle, approximates more to a straight line, which intersects the vertical line passing through the larynx, at a very acute angle. That is to say, in normal deglutition, the mass of food for the most part travels in a plane behind the opening of the glottis, but in paralysed conditions it travels for the most part in front of or directly over the opening. It is therefore easily understood that destruction of the epiglottis alone is a much less serious matter than muscular paralysis, so far as the likelihood of subsequent inhalation-pneumonia is concerned.

The chief morbid conditions involving the trachea and allowing passage of foreign substances into the lungs, are abnormal openings into the tube. Such are those produced voluntarily in suicidal attempts, or in tracheotomy and laryngotomy, and those produced by ulceration, pressure atrophy, etc., in malignant disease of the œsophagus or other parts in the neighbourhood, pressure of an aneurysm, and so on. In these cases the foreign substance is generally blood or some discharge, but particles of food or drink may pass into the trachea if there is a definite fistulous opening between it and the œsophagus.

Extension of a diphtheritic infection from the larynx to the lungs by way of the trachea must also be mentioned in this connection. Generally, a continuous diphtheritic membrane extends from the larynx downwards until it ends in a soft, but tenacious, purulent substance in the bronchi, but sometimes the membrane is confined to the larynx, or extends only for a short distance down the trachea. In either case the lung condition which subsequently supervenes is the same. It consists in a broncho-pneumonia, which only differs from that resulting from inhalation of other foreign substances in the fact that this form is associated with the presence of diphtheria bacilli, whereas broncho-pneumonia resulting from inhalation of other foreign substances is not.

Morbid conditions affecting the air-passages above the tracheal bifurcation may involve both lungs, but the right is more commonly affected by entry of a foreign body, such as a coin, owing to the anatomical arrangement of the parts. For the main axis of the trachea passes nearly through the centre of the entrance into the right bronchus, while it leaves the entrance into the left bronchus well on one side; and, besides, the diameter of the right bronchus is greater than that of the left. A foreign body will therefore naturally tend to fall into the right bronchus, and, practically, it is found that this almost always occurs.

(iii.) **The Bronchi.**—From the bifurcation of the trachea onwards morbid conditions may affect one lung alone.

There are many similarities between conditions affecting the main bronchi and conditions affecting the trachea. Thus, the right bronchus may present an ulcerated opening as the result of pressure by an aortic aneurysm, and blood entering the bronchus from the aneurysm may produce a lung condition hardly differing from that due to an abnormal opening into the trachea. Indeed the pulmonary results in the two cases are likely to be identical, for the blood which enters the right bronchus excites cough and is carried up into the trachea, whence it may readily be drawn into the left bronchus during inspiration.

In the case of the smaller bronchi, however, there are considerable differences, not only in the kinds of morbid condition by which they are affected, but also in the results produced by those morbid conditions. In connection with the smaller bronchi we have to consider (*a*) bronchitis, and (*b*) spasmodic asthma.

(*a*) *Bronchitis.*—As its name implies, bronchitis is an inflammation of the bronchi, and, like other inflammations, it may be produced by microbial or by non-microbial irritants.

Since the bronchi communicate freely with the outer air one would expect that a bronchitis from which micro-organisms are completely absent should be very rare, if indeed it existed at all. But it must be remembered that the air when it reaches the smaller bronchi is saturated almost completely with aqueous vapour, and has passed over a moist and sinuous path, which is lined by a ciliated epithelium. Hence, few of the micro-organisms which enter by the nose or mouth normally succeed in penetrating beyond the larger bronchi; as a matter of fact, expired air is singularly free from bacteria, and those which it contains have almost always been added to it in the pharynx, mouth, or nose during its passage outwards. Further, the cough and the excessive secretion of mucus which characterise bronchitis are means whereby such bacteria as have gained an entrance into the bronchi are expelled.

In spite of these undoubted facts, however, in bronchitis the ciliated epithelium of the bronchi is destroyed (or at least the cilia themselves are removed) and the tissue-resistance to invasion by bacteria is diminished. So that in a large number of cases the presence of micro-organisms in the finest bronchi, or even in the pulmonary alveoli themselves, can be demonstrated either microscopically or by culture. Moreover, absolute proof that bacteria in the inspired air succeed in reaching the terminal bronchioles is afforded by the numerous experiments in which pulmonary tuberculosis has been induced by causing an animal to respire air charged with tubercle bacilli.

The respiratory changes induced by bronchitis differ according as the larger or the smaller bronchi are principally affected, according to the characters of the bronchitis, according to the amount of lung tissue involved in the process. But certain characters of respiration are common to bronchitis generally.

In all cases of bronchitis the sounds heard on auscultation of the normal lung are modified, and especially by the fact that adventitious sounds are superadded. These are heard both with inspiration and expiration, are snoring (rhonchus), whistling (sibilus), or bubbling (râles) in character according to the amount of secretion present in the bronchi and its viscidity, and are lower or higher in pitch according as they are produced in larger or smaller bronchi. Further, expiration itself is altered apart from the existence of adventitious sounds. In the normal chest and with quiet breathing expiration is inaudible, but in bronchitis it is distinctly audible, and, in addition, it is commonly prolonged. The prolongation of respiration is due to the fact that air leaves the alveoli less rapidly than normal. This may be because the bronchial secretion presents a definite obstacle to recoil of the alveolar walls, but more often it means that their elasticity has become impaired because the bronchitis has led to an emphysematous condition of the lung after the manner that has already been described. The audibility of expiration in bronchitis depends upon the abnormal condition of the bronchial mucous membrane; the air, instead of passing over a smooth surface as in health, passes over one which presents irregularities owing to the congested state of the mucous membrane, the presence of exudation, mucus, etc. Where lung tissue is definitely involved, as in broncho-pneumonia, the audibility of expiration and the particular characters which are presented by it and by inspiration (tubular breathing), are due to the greater density of tissue lying between the bronchus and the chest-wall.

The rate of respiration in bronchitis, and the amount of dyspnœa experienced by patients, are very variable. In ordinary chronic bronchitis, in which the larger bronchi alone are as a rule affected, dyspnœa is generally absent and the rate of respiration is unaltered. But in acute bronchitis affecting the small bronchi of both lungs (bronchiolitis), and in broncho-pneumonia (capillary bronchitis, lobular pneumonia), the case is different. Respiration, in these forms of bronchitis, is rapid—thirty, forty, or more respirations per minute being often observed—and the dyspnœa may be as extreme as in stenosis of the larynx or trachea, though its characters are somewhat different. The same is true in plastic bronchitis, a very rare condition of which the pathology is unknown, but in which the exudation coagulates and forms a cast of portions of the bronchial tree. These casts are quite characteristic of the particular form of bronchitis, and portions may be expectorated after a severe fit of coughing; apparently they may be formed repeatedly, and they offer manifest analogies to the "false membranes" of diphtheria.

The increased rate of respiration in these cases probably has a multiple origin. In part it depends upon the fever by which acute (though not chronic) forms of bronchitis are accompanied; in part it is compensatory, a greater number of respirations being necessary to produce the same result, now that the aërating function of a portion of the lung has been abolished; and in part it is probably due to reflex stimulation of the respiratory centre by afferent impulses passing in the vagus from its terminations in the bronchial mucous membrane, for gentle[1] stimulation of the central end of the cut vagus below the origin of the superior laryngeal nerve quickens respiration.

In all cases of this description, however, it is difficult to decide how far the increased rate of respiration and the dyspnœa are of pulmonary, how far of cardiac, origin. Probably both pulmonary and cardiac conditions combine in producing the result. For not only do pulmonary conditions lead to cardiac changes, as we have already seen (p. 75), but also one of the most distressing forms of dyspnœa with rapid breathing occurs under conditions in which air can freely enter and leave the lungs (pulmonary embolism).

(*b*) *Spasmodic Asthma.*—Spasmodic asthma shows itself by the supervention, generally in the early morning, of an agonising dyspnœa. The rate of respiration is usually unaltered; the time occupied by the inspirations is perhaps shorter than normal, but expiration is greatly prolonged, and all the accessory muscles of expiration are called into play. Hence asthma is eminently an expiratory dyspnœa. In an uncomplicated case, this condition of respiratory distress lasts for two or three hours, and then gradually passes off, to be renewed, in all probability, on the following night. This may go on for two or three nights, and then, for a varying length of time, no attacks occur. During the interval between attacks the patient is in perfect health except for such symptoms as are due to muscular exhaustion, loss of sleep, etc., or are due to secondary cardiac or pulmonary changes as may have been induced by the attacks.

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[1] Stronger stimulation causes arrest of respiration, as does stimulation of the central end of either the superior laryngeal or the vagus above the point where it is joined by the superior laryngeal. For further details in reference to the effects of vagus stimulation upon respiration, text-books on physiology must be consulted.

The paroxysmal nature of spasmodic asthma is therefore one of its most marked characteristics, and this fact, together with the obvious impediment to expiration which obtains in an attack, are strongly in support of the view that asthma essentially consists in a spasmodic contraction of the unstriped muscular fibres in the walls of the bronchioles. It is now generally allowed that such a spasmodic contraction can experimentally be produced as the result of direct or reflex stimulation of the vagi. The fact, too, that depressant drugs—such as stramonium, chloroform, ipecacuanha in large doses, belladonna, etc.—are often of marked benefit in cutting short an attack, is further evidence in favour of this view.

But the pathology of asthma is not thereby fully elucidated. For, in the first place, it is not easy to understand how a spastic contraction of the bronchioles over the whole of both lungs can continue for hours; and, in the second place, even if this view be accepted, the cause which leads to the spastic condition is still unexplained.

For these reasons it has been suggested that asthma really consists in a congestion or inflammation of the whole bronchial mucous membrane, whereby the lumen of the smaller tubes is greatly diminished. It is certainly in favour of this view that in hay-fever, which is only a special form of bronchial asthma, the nasal mucous membrane is markedly congested and swollen, and that Störk claimed, by aid of the laryngoscope, to have seen the mucous membrane of the whole trachea and the opening of the right bronchus congested and swollen in a patient suffering from an attack of asthma. But it is so difficult, in view of the suddenness with which an attack generally comes on, and of the relations of asthma with migraine and epilepsy, to believe that a widespread inflammation or even congestion can be the immediate cause of asthma, that this explanation is even less satisfactory than the one which ascribes the attack to a muscular spasm.

There is no doubt, however, that in an attack of asthma, the patient's lungs are hyper-distended and his expiration is enormously impeded; his general aspect and examination of his chest are sufficient evidence of these facts. And since there is certainly no obstruction high up and in the larger air-passages, we are probably correct in concluding that the seat of obstruction is the smallest bronchioles. Cohnheim was inclined to believe that some cases of asthma are due to tetanic contraction of the diaphragm, though for the majority he believed that bronchial spasm is the explanation. With regard to tetanic contraction of the diaphragm, though theoretically it might be accompanied by a condition of asthma, I am not aware that there is any evidence, clinical or experimental, that this is actually the case, or that such a condition ever obtains in spasmodic asthma. On the whole, therefore, and in spite of difficulty, it is safest at present to hold that the attack of asthma is due to muscular spasm of the smallest bronchi, and that any congestion or inflammation of the bronchial mucous membrane that may be present is secondary.

Starting, then, from this standpoint, we have next to consider the conditions upon which the onset of the muscular spasm itself depends. Here we are upon very uncertain ground, for there is no disease in which so many different conditions may lead to attack; indeed, hardly two cases of asthma are alike in this respect. It was at one time thought that Charcot's crystals (p. 170), which are commonly found in the early expectoration after an attack of asthma, lead to onset of the attack by irritating the terminations of the vagi in the bronchial mucous membrane. But this view was abandoned when it was found that the crystals may often be found in the sputa of patients who do not suffer from asthma.

On the other hand, there is much to be said for the view that the disease is primarily nervous. In this respect its analogies with migraine and epilepsy—diseases that are admittedly nervous—are highly important. Thus all three conditions—asthma, migraine, epilepsy—occur in neurotic individuals, show a tendency to hereditary transmission, are liable to be called forth by indiscretions in diet, have relationships with gout, may be preceded by premonitory symptoms constituting a distinct "aura," whether this is generally the case as in epilepsy, frequently the case as in migraine, or sometimes the case as in asthma. Even more important, as showing this relationship, is the case, recorded by Salter, of an epileptic patient whose fits, after having set in with their usual premonitory symptoms, were on several occasions replaced by asthmatic paroxysms.

Next, it must be mentioned that asthma is in some cases directly traceable to an antecedent attack of bronchitis (whether primary, or occurring along with measles or whooping-cough) in a patient having no hereditary tendency to asthma. This fact suggests strongly that an impaired nutrition of the bronchi may play some part in the production of asthma. It is possible, in other cases in which this relationship with an antecedent lung affection is not recognisable, that there is a congenital hyper-sensitiveness of the bronchioles which is hereditarily transmitted. Upon this point, however, one can only speculate, though it would not be in disagreement with modern views of cell-nutrition.

Lastly, Marcet considers that the well-known fact, that a forced inspiration sometimes causes a temporary suspension of asthmatic spasm, is a proof that deficient aëration of the blood supplying the respiratory centres bears a definite relation to the causation of asthma.

The great difference between stenosis of the larynx or trachea and a stenosis such as we have presumed to exist in the attacks of bronchial asthma, lies in the fact that in laryngeal or tracheal stenosis there is difficulty both in inspiration and in expiration, whereas in asthma the difficulty essentially concerns expiration alone. This difference depends upon the fact that in the one case the obstruction is outside the thorax, whereas in the other it is within the thorax.

When the obstruction is tracheal or laryngeal, enlargement of the thoracic cavity with inspiration is without influence upon the degree of stenosis, but when the obstruction is within the thorax, and especially when it is situated in the bronchioles (as in asthma), the increase of negative pressure with inspiration tends to dilate the bronchioles and therefore to diminish the stenosis. Hence the different extent to which inspiration is impeded in the two classes of case.

But the direct converse obtains with regard to expiration. For when the obstruction is tracheal or laryngeal, violent expiratory efforts must tend to overcome the resistance and force the air within the chest past the obstruction, but when the obstruction is within the thorax, violent expiratory efforts only aggravate the mischief, by compressing the small bronchi and diminishing their lumen yet more. An analogous condition occurs in the case of patients with enlarged prostate; straining only forces the hypertrophied middle lobe of the gland yet more closely over the first portion of the urethra, so that it increases the difficulty of micturition, or may stop the flow of urine altogether.

(iv.) **The Pulmonary Alveoli.**—The alveolar conditions leading to disordered respiration are emphysema, obliteration of the alveolar cavity from within the lung, and collapse of lung.

(*a*) *Emphysema.*—Emphysema has already been considered at some length (p. 705), so we shall not discuss it further, but shall at once pass to consideration of conditions in which the alveolar cavity is obliterated by conditions acting within the lung.

(*b*) *Obliteration of the Alveolar Cavity from within.*—Under this heading come such conditions as croupous pneumonia, broncho-pneumonia, tuberculosis and other forms of specific broncho-pneumonia, abscess, new-growths in the lung, hæmorrhagic infarct, pulmonary apoplexy, œdema of the lung. Widely differing as they are in their histological characters and in the morbid conditions upon which they depend, widely differing according as they destroy and replace the lung tissue (*e.g.*, new-growths, tuberculosis, abscess) or are temporary additions to the lung tissue (*e.g.*, croupous pneumonia, œdema), they yet all agree in the fact that they reduce the amount of lung available for the exchange of gases between the outer air and the blood. This being the case, they must, of necessity, throw extra work upon the alveoli that are still capable of exercising their function. And the degree to which that extra work shows itself by disordered respiration must depend—at least, in part—upon the amount of lung tissue that has been rendered functionless.

The condition best exemplifying the statement just made is croupous pneumonia. In this disease a considerable proportion of the total lung area—one or more lobes—is within a few hours converted into a solid mass, and becomes useless so far as aëration of blood is concerned, owing to the outpouring and coagulation of a copious inflammatory exudation into the air-sacs. The result is that the remainder of the lung becomes hyper-distended (as shown by the note which it yields on percussion), and the rate of respiration is enormously increased. The respirations themselves are shallow, but they may number thirty, forty, or more in the minute. There is often no feeling of distress, but the bluish coloration of the lips, cheeks, and ears shows that the blood is deficiently aërated. That this increased frequency of respiration is not merely associated[1] is clearly indicated by the fact that the rate of respiration is increased quite out of proportion to the increased rate of heart-beat. The ratio between these two is no longer the normal three or four to one, but rises to two to one or higher, and in some cases, where both lungs are affected, respirations are even more frequent than heart-beats.

But however probable it seems that this increased frequency of respiration in pneumonia is compensatory, it is impossible to accept this view as a full and complete explanation. For it is one of the most striking phenomena of the disease that directly the critical fall of temperature has taken place, the ratio between rate of respiration and rate of heart-beat returns to the normal. And this, though physical examination, and actual inspection in fatal cases, proves conclusively that the amount of solidified lung is still the same as before the crisis. In part, no doubt, the increased frequency of respiration is also febrile. But even then the phenomena are not fully explained. For in the case of pulmonary tuberculosis we may have a solidification of lung quite as extensive and a fever quite as high, but the normal ratio of respiratory frequency to frequency of heart-beat is not disturbed as it is in pneumonia.

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[1] See below, p. 738.

There must consequently be some other factor or factors entering into the process. Of these, the suddenness with which the solidification of lung is brought about seems to play a highly important part. In the case of pleural effusion we know that the rate of respiration is more readily quickened by a rapid outpouring of fluid, though the total quantity be small, than it is by a gradual outpouring of a far larger quantity. And analogous examples showing the effect of the time-factor in determining the resulting phenomena might easily be multiplied. Since, then, it takes tuberculosis at least as many weeks to produce the same degree of pulmonary solidification that croupous pneumonia produces in hours, it is intelligible that the respiratory phenomena should be different in the two diseases, and, in particular, that the respiratory function should be disordered to a greater extent in pneumonia.

At this point we are left in the region of surmise. For the need of compensation, the fever, the conditions induced by rapid onset of the disease can only modify respiration by way of the respiratory centre, and of the changes occurring here we are completely ignorant.

It is unnecessary to discuss the other conditions which have been mentioned as leading to obliteration of the alveolar cavity from within. Nor is it necessary to refer to the pneumokonioses, in which a sub-inflammatory condition of lung, accompanied by formation of much fibrous tissue, is produced by inhalation of those various forms of dust which have already been mentioned as causing abnormal pigmentation of lung. For they all act essentially in the same way as tubercular infiltration or croupous pneumonia. They cause hyper-distension (perhaps also, in the case of the more chronic diseases, hypertrophy) of the alveoli into which air can still enter. They increase the frequency of respiration to a greater or less degree according as the amount of lung involved is greater or less, according as the disease is produced with greater or less suddenness, according as it is more or less accompanied by fever. They modify the depth of individual respirations, making them shallower if the amount of lung involved is great or respiratory movements are accompanied by pain, making them deeper if the amount of lung involved is not great and if respiratory movements are painless. Speaking generally, the depth of individual respirations varies inversely with the frequency of respiration; but when the disease is not extensive, depth of inspiration and frequency of respiration may both be slightly increased.

(*c*) *Collapse of Lung.*—In collapse of lung, as in diseases where there is obliteration of the alveoli from within, air fails to reach the air-sacs. Since, too, both conditions agree in that they may involve amounts of lung varying from a few lobules to whole lobes or even a whole lung, the actual changes in respiration brought about by them are, in the main, identical. Such differences as obtain depend, not upon the collapse or the obliteration from within, as such, but upon the causes leading to those conditions. It is unnecessary, therefore, to discuss the respiratory changes caused by collapse of lung. But a few words must be said as to the manner in which collapse of lung is produced.

The distension with air of normal lung is brought about by the first inspirations after birth. In a still-born child the lungs are completely airless, and sink in water like lung tissue which has become solid by obliteration of alveoli from within. This condition, however, is not termed collapse, but *atelectasis.* In individuals who have once breathed, atelectasis is extremely rare, except in the case of premature and weakly infants, and in the large majority of cases, an airless condition of lung tissue means that air has been removed from previously distended air-sacs, not that it has never reached them; in other words, it means that we have to do with collapse, not with atelectasis.

The conditions leading to collapse of lung are essentially two: (1) pressure on the alveoli from without, (2) obstruction to bronchi. The ultimate process whereby air is removed from the alveoli is probably the same in both cases, and as it will be necessary to discuss the effects of morbid pleural conditions upon respiration, we shall confine our attention here to collapse of lung brought about by obstruction of bronchi. The chief condition which leads to obstruction of bronchi being bronchitis affecting the smaller tubes, collapse of lung and broncho-pneumonia generally occur together.

For a long time collapse of lung was explained by aid of a theory formulated by Gairdner, and known as the "ball-valve" theory. Gairdner's theory was a converse of the explanation given by Laennec for emphysema. It assumed that when a plug of secretion is in a small bronchus, it is drawn more closely to the bronchial wall in inspiration and pushed away during expiration, and hence it was concluded that more air leaves the alveoli with which the bronchus is in connection, during expiration, than enters it during inspiration. This theory is now of historical interest only.

At the present time it is generally accepted that collapse is produced because the air, formerly contained in the alveoli communicating with the obstructed bronchus, has been removed by the blood. This was conclusively proved by Lichtheim nearly twenty years ago. He completely obstructed bronchi in rabbits by placing in them plugs which swelled with the moisture, and found that a typical collapse was produced of that portion of lung supplied by the occluded bronchus. Finding that pure oxygen is removed from the alveoli more rapidly than atmospheric air, and that the same is true (though to a less degree) in the case of carbonic acid, while pure nitrogen is removed less rapidly than atmospheric air, he concluded that in collapse the oxygen of the contained air is removed first, then the carbonic acid, and last of all the nitrogen. But whether this be so or no, there is no doubt that in collapse all air is removed even to its last traces, so that the alveolar walls ultimately lie in contact, or at most are separated by a small quantity of fluid or a few cells.

*Method whereby Air is removed from the Alveoli in Collapse of Lung.*—The actual manner whereby air is removed from the alveoli in the production of collapse will, at no distant date, form part of the whole controversy as to whether the exchange of gases in the lung between blood and alveolar air is a physical or a vital process. The majority of authors believe that this exchange is a physical one of diffusion, and depends upon the tensions of the oxygen and the carbonic acid on the two sides of the membrane formed by the alveolar epithelium. In accordance with this physical explanation of normal respiration, Lichtheim believed, and most authorities follow him in this respect, that the removal of air from the alveoli, in the production of collapse, is carried out by diffusion, aided by the normal elasticity of the lung.

The common explanation of collapse is therefore as follows. As the intra-alveolar air is removed by its diffusion into the blood of the alveolar capillaries, the intra-alveolar pressure falls. At a certain point, diffusion of the contained gases into the blood would cease were it not that the elasticity of the alveolar wall keeps the intra-alveolar pressure constant, and is not exhausted until the last traces of air have been removed.

But serious objections have lately been raised to the commonly-received view as to the exchange of gases in the normal lung.

It was shown by Biot's and Moreau's work that the oxygen tension in the air-bladder of fishes (which is morphologically homologous with the mammalian lung) varies considerably in different species, and according to the depth at which the fish is placed under water. It was shown further that the tension of oxygen in the air-bladder, amounting, as it may do, to 80 per cent. of the total gas in the bladder, is far greater than the oxygen tension in the water, which, at most, cannot exceed 21 per cent., *i.e.*, the proportion of oxygen contained in the atmosphere. Hence one cannot regard the oxygen in the air-bladder of fishes as having arrived there by a simple process of diffusion; it must have been actively secreted into the air-bladder.

Bohr corroborated the above results, and showed further that the process is under control of the central nervous system, for secretion of oxygen does not take place when the branches of the vagus nerve supplying the air-bladder are cut. In mammals, Bohr maintains that the oxygen tension of arterial blood is greater than the oxygen tension of the alveolar air, and Haldane and Lorrain Smith support him fully in his contention.

Haldane and Lorrain Smith, as the result of numerous experiments on different animals, including man, hold that the oxygen tension of arterial blood has been hitherto under-estimated owing to oversight of the fact that a considerable and all-important dissociation of oxygen from oxyhæmoglobin, and its fixation in some firm combination, takes place within the first few seconds after removal of blood from the body. By improved methods they have shown that the oxygen tension of arterial blood is far greater than is generally taught, and, in most cases, is considerably higher than the oxygen tension of the inspired air. Collating their results with those of Löwy, who found by careful estimation that the tension of oxygen in the alveolar air is only equal to a little more than one-eighth of an atmosphere (actually 13·15 per cent.), they maintain that diffusion alone is insufficient to explain the passage of oxygen through the alveolar epithelium. Thus, in their last paper,[1] they give experiments showing that in man the average oxygen tension of arterial blood is 38·5 per cent. of an atmosphere, while the oxygen tension of inspired air is 19·7 per cent., and the intra-alveolar tension of oxygen (Löwy) is 13.

Here we must leave the question of absorption of oxygen by the lungs. The controversy is no more settled than the allied controversy as to the mode of lymph-formation; and in the one case, as in the other, personal estimation of the value of given experiments comes into play. But it seems to me that the results of Bohr and of Haldane and Lorrain Smith will need strong refutation if the present physical explanation of gas exchange in the lungs is to hold its ground.

In view, therefore, of the uncertainty which obtains as to whether, under normal circumstances, gaseous exchange between the blood and the intra-alveolar air is one of secretion or one of simple diffusion, it is well to keep an open mind with regard to the manner in which air leaves the alveoli in the production of pulmonary collapse. It may be that the explanation commonly given is the correct one, but it is obviously possible that the same ultimate result could be attained if the alveolar or capillary epithelium continued to secrete air into the blood, while at the same time it ceased to obtain a fresh supply, owing to obstruction of the bronchus with which the alveoli concerned are in connection.

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[1] *Journ. of Physiol.*, vol. xxii. No. 3, November 20, 1897.

(v.) **The Pleuræ and Pleural Cavities.**—Morbid conditions of the pleuræ and pleural cavities play a very important part in determining abnormalities of respiration. For not only is it necessary to normal respiration that the visceral and parietal surfaces of the membrane shall glide smoothly upon one another, but it is also necessary that the two layers shall be in contact. The morbid conditions that we shall have to consider are therefore (1) those in which the pleural membrane is altered; (2) those in which the pleural layers are no longer in contact.

(A) **The Pleuræ.**—Of morbid conditions affecting the pleuræ themselves, inflammation is by far the most important. But we shall not discuss pleuritis (pleurisy) here to any extent, because the remarks made when discussing pericarditis, as to its causes, the appearance of the membrane, the formation of "lymph," the "friction rub," the beneficial results of a small amount of effusion, the changes leading to the formation of adhesions, etc., apply equally well in the case of pleurisy. It is sufficient to state that the respiratory modifications caused by pleurisy itself —apart from those due to collection of fluid or to accompanying lung conditions—consist in a shallowness of respiration, accompanied at the end of inspiration by a sudden "catch in the breath." This modification is determined by the pain induced by the respiratory act, whence it follows that respiratory modifications are marked according as the onset of the pleurisy is acute. On the other hand, when the pleural inflammation is very chronic, as in many cases of tuberculosis, it may never cause the patient any pain, and therefore may have been unaccompanied by any respiratory modification at all. This explains why the existence of a pleurisy in pulmonary tuberculosis is often unsuspected until the effusion poured out has accumulated to such an extent that it interferes directly with respiration by its mechanical effects.

When the pleural layers, as the result of antecedent inflammation, have become joined over a greater or less extent of their surfaces by the formation of fibrous adhesions, gliding movements between the lung and the thoracic wall are of course proportionately impeded. This throws extra work on the muscles concerned in respiration, but it does not of itself introduce any considerable respiratory modification; the modified respiration which undoubtedly obtains in such cases is essentially due to the pulmonary condition underlying the pleurisy. Since, however, the adhesions are constantly being stretched by the respiratory movements, and are themselves a source of irritation, it is common, even in the case of dense adhesions, to find some evidences of active inflammation. As a rule, these are microscopic, and are represented by small local collections of migrated leucocytes, but the frequency with which repeated attacks of pleurisy occur in the same patient, and more or less constantly over the same region, shows that it is rare for the pleural inflammation to become perfectly quiescent. In this respect widespread adhesion of the pleural layers is more satisfactory than the presence of isolated bands of adhesion, for in the former case, movement, and the irritation to which movement gives rise, are more limited.

(B) **The Pleural Cavities.**—The formation of adhesions between the pleural layers obliterates the pleural cavity to a corresponding extent, and this of itself, as has just been said, is relatively unaccompanied by respiratory modification. But the case is different when the pleural layers are separated, for then respiration is, as a rule, profoundly altered. Separation of the pleural layers may depend upon the presence between them of fluid or of air; we therefore have to consider (1) pleural effusion, and (2) pneumothorax. Afterwards a few words will be said concerning (3) absorption from the pleural cavity.

(1) *Pleural Effusion.*—An effusion into the pleural cavity is generally either the result of inflammation, when the fluid may be serous or purulent (empyema), or the result of venous congestion, when it is always serous. One of the best-marked examples of an inflammatory effusion is frequently seen in cases

of pulmonary tuberculosis, and is called forth by the irritation of the pleura by hard sub-pleural tubercles. Of the same nature is the pleural effusion that often accompanies the presence of new-growths in the lung or the thoracic wall; the fact that in these cases the exudation is commonly hæmorrhagic is unimportant pathologically, though highly important diagnostically. Empyemata are typical inflammatory effusions, and are commonly sequels of some definitely inflammatory condition of the lung, such as croupous pneumonia or broncho-pneumonia. In their causation *M. pneumoniæ* plays a prominent part. Pleural effusions, the result of venous congestion, are best seen in the case of cardiac disease and those morbid conditions which are liable to be accompanied by hypostatic congestion of the lungs. Besides these causes of pleural effusion, it must also be mentioned that rupture of blood-vessels, whether aneurysmal or healthy, whether as the result of disease or of injury, may fill the pleural cavity with blood. Rare conditions, such as that in which a hydatid cyst ruptures into the pleural cavity, do not call for special remark.

The effects of a pleural effusion upon respiration are brought about by the pressure which that effusion exerts; the nature of the effusion itself is practically of no importance. Not so, however, the rapidity with which the effusion is poured out. In this respect the pleural and pericardial cavities are closely analogous. We have seen that the rapid outpouring of 150–200 c.c. of blood into the pericardial cavity, as the result of rupture of an intra-pericardial aneurysm or rupture of the heart wall, causes profound (and fatal) modification of cardiac function, whereas gradual accumulation of serous fluid may go on for weeks, and until it is measured by pints, with far less serious results. The same is true of the respiratory function when the pleural cavities are involved, though, of course, the amounts of fluid concerned in this case are greater, and the constitutional disturbance is generally less. But, nevertheless, sudden effusion of blood or outpouring of inflammatory effusion causes a respiratory distress which is not seen in the case of chronic effusion until a far larger quantity of fluid has collected in the pleural cavity.

A pleural effusion quickens respiration and renders it shallow. This result is due to two causes: firstly, the pressure exerted by the fluid on the lung; secondly, the pressure exerted on the heart.

In the case of the lungs, a distinction must be made between the lung on the same side as the effusion and the lung on the other side. For though the thorax is usually spoken of as one cavity, the solid mediastinal tissues divide it into two, more or less, independent cavities. Hence pressure-changes occurring in one pleural cavity are to a certain extent shut off from the rest of the thorax, and the effects of a localised pleural effusion are different in the case of the two lungs.

On the unaffected side respiratory movements are intensified, and the lung undergoes hyper-distension owing to the necessity which has arisen for an increased activity of the sound organ. On the affected side the pressure exerted by the fluid leads to an airless and bloodless condition of the lung (carnification), which is more or less extensive according to the amount of fluid and the pressure which it exerts, and which may therefore be confined to a few lobules, or may involve the whole lung. In the latter case the lung lies close to the spinal column, and is hardly recognisable as lung at all. On this side, too, respiratory movements are impaired and may be absent, and auscultation shows that air enters the lung less freely than normal, or not at all. Nevertheless, the whole lung on the affected side is not, as a rule, rendered functionless; the upper lobe commonly partakes of that hyper-distension which occurs on the sound side. Where both pleural cavities are the seat of effusion, both lungs are in part collapsed, in part hyper-distended; thus, it is common after death from cardiac failure to find the pleural cavities containing one or two pints of fluid, the bases of both lower lobes collapsed, and the upper lobes hyper-distended or even emphysematous. How far the hyper-distension of lung is able to compensate for the lung tissue which has been rendered functionless, depends upon the amount of effusion, the rapidity with which that effusion has been poured out, and, especially, upon the condition of the pulmonary tissue which is called upon for extra exertion. It follows, therefore, that the degree to which respiration is quickened and rendered shallow by a pleural effusion depends upon these same factors.

In the case of the heart, the effects of a pleural effusion are obscure, but they must be of great importance. For not only is the heart displaced whenever a considerable effusion takes place into either pleural cavity, but also the alteration of intra-thoracic pressure must interfere with normal filling of the heart, and the compression of lung on the affected side must interfere with passage of blood through the corresponding pulmonary capillaries. It would not be advisable to discuss here the methods in which these factors may act, for the whole question is very complicated. But that the dyspnœa accompanying a considerable pleural effusion is largely of cardiac origin, is amply proved by the fact that respiration is immediately relieved by giving exit to the fluid, though it is certain that the compressed lung tissue does not resume its normal function till much later, and in some cases does not resume it at all.

The cyanosis which often accompanies pleural effusion calls for no special remark; it is partly of cardiac, partly of pulmonary origin.

(2) *Pneumothorax.*—In pneumothorax the visceral and parietal layers of pleura are separated by air, and the normal negative intra-pleural pressure is replaced by atmospheric or even by a positive pressure. The essential factors concerned in the production of pneumothorax are the elasticity of lung tissue and the intra-pleural negative pressure. If in a healthy person the pleural cavity is by any means brought into direct connection with the atmosphere, the pressures inside and outside the pleural cavity are immediately equalised by the elastic contraction of the whole lung. Moreover, since it is owing to the existence of a negative intra-pleural pressure that air enters the lung with normal inspiration, it follows that respiratory movements become valueless so far as the affected side of the thorax is concerned, and that the lung on this side takes no further part in respiration. Hence, in a moment, an enormous increase of work is thrown upon the unaffected lung, with the result that onset of the pneumothorax is accompanied by agonising dyspnœa; and since

even the dyspnœic breathing of one lung is unable to fully compensate for the functionless condition of the other, there is intense cyanosis. Besides these symptoms, there are those attributable to profound shock.

Such symptoms as have just been described as occurring in a healthy person on the production of a pneumothorax are not, however, always seen in disease. For if, as is very generally the case, pneumothorax supervenes during the course of pulmonary tuberculosis, it may happen that so much of the lung has become bound down to the chest wall as the result of antecedent pleurisy, that contraction of the lung to undistended volume cannot take place. Under these circumstances formation of a pneumothorax may be unaccompanied by any important symptoms. Usually, however, some condition intermediate between these two extremes is met with, and in the cases definitely recognised during life as pneumothorax, a sudden onset of dyspnœa with cyanosis, severe pain, and shock is noted.

Though the symptoms accompanying pneumothorax are, in the large majority of cases, far more severe than those accompanying pleural effusions, owing to the suddenness with which pneumothorax is produced and the extent of lung which it often involves, there is a general similarity between the effects of the two conditions. This is especially noticeable when the air in the pleural cavity is under pressure, for then the heart will be as greatly displaced as it is in cases of large pleural effusion. Considerable displacement of the heart is also seen when the intra-pleural pressure is merely atmospheric owing to the traction exerted by the other lung. It is necessary to note, however, that in cases where the pericardium has become closely attached to the thoracic wall or to the pleura as the result of antecedent inflammation, displacement of the heart cannot take place.

The chief causes of pneumothorax are rupture of the wall of a superficial vomica, bursting of an empyema into a bronchus, laceration of the lung by a fractured rib, penetrating wounds of the chest wall. The actual distress accompanying any of these accidents varies considerably; in the case of a fractured rib or of a penetrating wound of the chest wall, it is almost always very great, not only because the patient's pleuræ are commonly healthy, and therefore the whole of one lung suffers contraction, but also because the pneumothorax is liable to be complicated by intra-pleural hæmorrhage from laceration of the lung. If pyogenetic micro-organisms have gained access to the pleural cavity, the pneumothorax is likely to become converted into a pyopneumothorax. Indeed, in most instances, it is a pyopneumothorax from the first, for pulmonary tuberculosis and empyema account for an overwhelming majority of the cases of pneumothorax. It is mainly in surgical cases that one meets with a pure pneumothorax, and then it does not usually remain so for long, since inflammatory changes take place in the pleura, whether they go on to the formation of pus or no.

The question whether the pressure within a pneumothorax is atmospheric, or is positive, depends upon the nature of the opening into the pleural cavity. If the opening is free and not valvular, air enters and leaves the pleural cavity by the opening with each respiration, and the intra-pleural pressure is therefore atmospheric. But if the opening is valvular, and of such a kind that it allows entrance of air into the pleural cavity with inspiration, but is a bar to its exit during expiration, air collects in the pleural cavity until the pressure which it exerts upon the valve is sufficient to prevent further entrance of air. When we remember the force exerted by the inspiratory muscles, it is clear that the pressure that can thus be produced in the pleural cavity may be very considerable.[1]

(3) *Absorption from the Pleural Cavity.* — A lung that has suffered contraction as the result of pneumothorax, or has been compressed either in this way or by a pleural effusion, is not

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[1] The most important experimental work upon pneumothorax of recent years has been done by Rodet and Pourrat, Rodet and Nicolas, Aron, and Sackur. Rodet and Nicolas found that the composition of a gas injected into the pleural cavity undergoes rapid modification. Thus they found that the gas in the pleural cavity twenty-two minutes after injecting pure $CO_2$, consisted of 3·4 per cent. $CO_2$, 18·2 per cent. O, 78·4 per cent. N. They concluded that the change is due to diffusion between the gas in the pleura and the gases of the blood, *not* the intra-alveolar gases. For when they introduced atmospheric air into the pleural cavity and caused the animal to inhale oxygen, they found no marked increase in the oxygen content of the intra-pleural air.

necessarily injured permanently. If a negative pressure becomes again established in the pleural cavity, before inflammatory and other changes have had time to damage the lung tissue irretrievably, the lung again expands with the inspiratory movement of the chest wall and resumes its function. Whether this fortunate termination obtains or no, depends upon a number of circumstances, of which the length of time during which the lung has remained functionless and the pressure to which it has been exposed, are among the most important.

If the lung is to resume its function this can only be brought about by closure of the pleural opening and removal of the air or liquid in the pleural cavity. Putting on one side aid given by surgical means, removal of the air or liquid is carried out by a process of absorption. Removal of fluid from the pleural cavity we have already discussed sufficiently along with absorption of fluids generally (pp. 248 and fol.), and have seen that it takes place certainly by way of the lymphatics, and probably also, in some instances, by way of the blood-vessels. With regard to the removal of air, there is no doubt that absorption takes place from the healthy pleural cavity with extraordinary rapidity, but whether the air is removed by a process of simple diffusion, as is generally believed, is, in my opinion, as uncertain as it is in the analogous case of pulmonary collapse. When the pleura is not healthy, as in most cases of pneumothorax occurring in the course of disease, it is in the highest degree probable that absorption does not take place with the same degree of rapidity. Upon this point we have no definite experimental evidence; nevertheless, the fact that pneumothorax in which the contained air is under considerable pressure is a fairly common pathological condition, whereas it is almost impossible to produce experimentally a pneumothorax of this description in an animal with healthy pleural membranes, owing to the rapidity with which the air is absorbed after its introduction into the pleural cavity, is strong evidence in this direction.

**II. Effects of Changes in Respiratory Movements upon Respiration.**—Since respiration is essentially a muscular act, interference with any of the muscles concerned in respiration is of importance in considering the pathology of respiration. It is astonishing, too, how many parts that have no primary connection with respiration are indirectly concerned in the act. Thus, one cannot easily consider the perinæal structures as respiratory, and yet any inflammatory process going on in this region, *e.g.*, an ischio-rectal abscess, often has a profound though indirect effect upon respiration, rendering it shallower and more rapid than normal, owing to the pain caused by compression of the inflamed tissues when a considerable descent of the diaphragm takes place. For the same reason the breathing becomes largely of a costal type. In the case of peritonitis, a respiratory modification of this kind is even more marked, so that a complete absence of diaphragmatic breathing becomes an important diagnostic sign of the condition. In the cases mentioned, the altered type of breathing is induced to a large extent unconsciously on the part of the patient, but that it is principally the pain which leads him to make the change is shown by the fact that, if he be put deeply under the influence of opium, diaphragmatic breathing is generally resumed. Nevertheless pain, as such, does not afford the whole explanation, for a patient with generalised peritonitis, though in a condition of profound shock (or more probably *because* he is in such a condition), may be unconscious of pain, and yet his breathing is purely costal, very rapid, and very shallow. So that we must conclude that the passage upwards of afferent impulses inhibits diaphragmatic action, whether those impulses affect consciousness or not. In some cases of peritonitis the change is no doubt in part dependent upon the fact that the muscular bundles of the diaphragm themselves share in the inflammation and their contractility is impaired.

Apart from cases of this description in which respiration is modified indirectly, there is a considerable number of conditions in which it is modified because of some alteration in the bony framework of the thorax or in the true respiratory muscles. To a large extent bony and muscular changes go together, but in many instances they are independent, or the one change is definitely antecedent to the other. It will, therefore, be convenient to consider them separately.

(i.) **Respiratory Modifications due to Morbid Conditions of the Ribs and Dorsal Vertebræ.**—We may leave entirely on one side respiratory modifications seen along with fracture of the ribs, for these are identical with the modifications accompanying acute pleurisy; indeed, the actual respiratory changes seen in cases of fractured rib are principally due to a coincident pleurisy. So also it is not necessary to discuss the respiratory modifications seen at times in cases of advanced lateral or anterior curvature of the spine. For in these cases the thoracic capacity is diminished, as it is in cases of pleural effusion (though much more gradually), and the mobility of the chest wall is impaired, so that respiration assumes similar changes, and becomes shallower and more frequent than normal. But there still remain conditions in which the chest wall is more rigid than normal, and in which, therefore, enlargement of the thorax with inspiration, and diminution in size with expiration, are impaired.

The chief conditions in which increased rigidity of the chest wall is seen, are old age and emphysema. In the case of old age, the change is a primary one, and chiefly consists in that calcification of the costal cartilages which is a natural accompaniment of old age. In health, lessened mobility of the ribs produced in this way is relatively unimportant, for a greater capacity of the thorax can easily be obtained by a slightly deeper descent of the diaphragm. But in disease this immobility of the thorax may become extremely important. For whether the particular malady affects the lungs or no, the increased respiratory exertion induced by the diminished mobility of the thorax is a cause of exhaustion; and when, as is so commonly the case in old persons, the lungs themselves are primarily or secondarily involved, diminished mobility of the chest wall may play a highly important part in bringing about a fatal termination, or, at any rate, in retarding convalescence.

In emphysema the thorax assumes a characteristic "barrel" shape. The concavity forwards of the vertebral column in the dorsal region becomes increased, the normal oblique position of the ribs is exchanged for a more nearly horizontal one, and the mobility of the ribs themselves is diminished. The reason of these changes lies in the increased volume of the lungs in emphysema, the expiratory dyspnœa which that condition induces, and the relative chronicity of the whole disease. The thoracic change is therefore secondary to the pulmonary change though it runs on parallel lines. The effect upon respiration of the altered shape and mobility of the chest wall in emphysema is insignificant compared with the effect of the emphysema which calls it forth, but in advanced stages of the disease the additional difficulty placed in the way of respiration becomes of great practical importance.

(ii.) **Respiratory Changes due to Abnormal Action of Respiratory Muscles.**—Respiratory modifications due to mechanical interference[1] with action of the diaphragm and intercostal muscles do not call for more than brief mention here, though, clinically, they are of considerable importance owing to the distress which they occasion the patient. The chief conditions that embarrass respiration in this way are ascites, tympanites, presence of an intra-abdominal growth, and all allied abdominal conditions. They act partly by direct encroachment upon the thoracic cavity, partly by offering an abnormal resistance to descent of the diaphragm during its inspiratory contraction, and probably to a very considerable extent by way of the vascular embarrassment to which they give rise, and the production of a cardiac dyspnœa.

Besides mechanical interferences with respiration of this nature, there are also those due to developmental defects in the diaphragm, and inflammatory conditions of the intercostal muscles. Such are congenital absence of part of the diaphragm, and the invasion of intercostal muscles by *Trichina spiralis* (Cohnheim). These conditions do not call for further remark.

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[1] From the observations made by Fitz on large numbers of individuals unaccustomed to wear constricting dress, it appears that the difference between the modes of respiration of civilised men and women depends upon the fact that civilised woman constricts her abdomen, and impedes descent of her diaphragm. Where this is not the case, respiration is about equally balanced between the costal muscles and the diaphragm, and little or no difference is observable between the modes of respiration in the two sexes.

Of quite a different order are respiratory modifications due to paralysis of the true respiratory muscles. Here we omit mention of paralyses leading to inhalation-pneumonia, for they have already received sufficient attention; we are only concerned with paralysis of the intercostal muscles and the diaphragm.

Paralyses of respiratory muscles are probably, in all cases, primarily nervous. Sometimes the nervous affection is clear, as, for example, when paralysis follows some injury or other surgical affection involving the spinal cord, but in other instances,—for example, Landry's acute ascending paralysis,—though implication of the nervous system cannot be doubted, histological examination has hitherto failed to demonstrate any nerve changes. Besides the examples just given, respiratory disorders follow whenever the intercostal muscles or diaphragm become involved in such paralytic conditions as progressive muscular atrophy, diphtheritic paralysis, and lead palsy.

In cases of this description the extent to which respiration is altered, depends upon the number of muscles involved and the degree to which they are affected. When the spinal cord is injured above the origin of the phrenic nerves, death necessarily and immediately follows, but a lesion below the origin of these nerves is not incompatible with life. On the other hand, in progressive muscular atrophy, the paralytic condition of respiratory muscles is less complete, but it affects both intercostal muscles and diaphragm. The patient with this disease does not die because all his respiratory muscles are completely paralysed, but because the impaired respiratory movements have allowed the supervention of some inflammatory condition in the lung, with which the weakened respiratory apparatus is unable to cope. Concerning the characters of the respiration in these different cases it is unnecessary to speak.

Closely allied with paralytic affections of the true respiratory muscles are those in which the extraordinary muscles of respiration are affected. Thus in primary progressive myopathic (pseudo-hypertrophic) paralysis and in the atrophic form of the same disease (Erb's paralysis) the pectorales major and minor, the serrati, the infra- and supra-spinati, the trapezii, and other muscles become paralysed and wasted, with the result that pulmonary affections assume a proportionately greater importance. Indeed, pulmonary affections are the commonest causes of death in all cases in which there is impairment of the musculature concerned in respiration, whether ordinary or extraordinary.

Lastly, a word must be said concerning respiratory modifications occurring in cases of hemiplegia. When, for example, a cerebral apoplexy interferes with the passage of nervous impulses between one half of the body and the opposite cerebral cortex, there is no doubt that the corresponding half of the diaphragm and the respiratory muscles on the corresponding side must be affected. But owing to the law that those muscles which are normally used in concert, recover soonest and most completely after a paralytic stroke (probably because they are innervated from both cerebral hemispheres), hemiplegia is not accompanied by the changes that one might at first expect. It is only in the rarest instances, and very early after the attack, that the intercostal muscles on the affected side are seen to be completely paralysed. According to Grawitz, however, it is very common to meet with a retarded expansion of the chest on the affected side, even during unconsciousness, but this is only temporary. The actual changes in respiration observed when a paralytic patient is unconscious after an attack are therefore different from those occurring with definite paralysis of intercostal muscles such as is seen in fracture of the lower cervical or upper dorsal vertebræ. The respirations are slow and very deep, while the passage of air over the pendulous and paralysed soft palate causes the characteristic "stertorous breathing" of unconsciousness. The altered rate and depth of respiration in these cases depends upon an altered condition of the respiratory centre, and not upon altered muscular action as such.

**III. Respiratory Modifications due to Circulatory Disorders.**—We shall not refer in detail to the respiratory modifications resulting from impaction of an embolus derived from the systemic (*e.g.*, uterine) veins in a main branch of the pulmonary artery, for they practically consist only in an intensely rapid and a deepened respiration until the patient is moribund; immediately before death they become sighing in character and infrequent. The circulatory changes produced by a large pulmonary embolism have already been mentioned (p. 109). We shall therefore pass at once to consideration of the respiratory distress that is so common a symptom in cardiac disease; it will then be convenient to discuss the pathology of renal dyspnœa and heat dyspnœa, though, strictly speaking, they do not come under the same heading.

Though the attacks of respiratory distress occurring in cardiac disease and in uræmia are often spoken of as "cardiac asthma" and "renal asthma," and though, in uræmia particularly, the symptoms may bear a marked resemblance to those of an attack of spasmodic or bronchial asthma, it is necessary to distinguish the conditions very sharply. For this reason the terms "cardiac dyspnœa" and "renal dyspnœa" will alone be used.

(i.) **Cardiac Dyspnœa.**—Cardiac disease is accompanied by modified respiration, both in its earlier and in its later stages; but the pathology of the respiratory changes is different in the two cases.

In early cardiac disease, shortness of breath is one of the most constant symptoms, but it only shows itself when the patient is undergoing muscular exertion (as when he is walking fast, or up hill), or when the heart beats rapidly from some mental cause, such as fright. The shortness of breath in these early cases of heart disease hardly amounts to dyspnœa; it is better described as "tachypnœa," for the rate of respiration is the main factor changed.

Tachypnœa upon exertion in early cardiac disease is comparable with the increased frequency of respiration seen in a healthy person when undergoing muscular exertion, only it is called forth more readily. We might consider that the readiness with which tachypnœa occurs in a cardiac patient, depends upon the fact that the impaired cardiac function does not allow the blood to be brought to the lungs with sufficient rapidity to ensure a proper oxygenation. That is to say, we might consider the tachypnœa as compensatory for an impaired action of the heart. This may be so in part, but it cannot be the whole explanation. For, in the first place, the rate of heart-beat in such cardiac patients is itself disproportionately increased by slight exertion; and, in the second place, the amount of oxygen which a given volume of blood can take up is practically constant and independent of the amount of oxygen presented to the hæmoglobin, so long as sufficient oxygen is presented for its saturation.

Now, the air-passages being free in cases of slight or early cardiac disease, and the amount of oxygen in the lungs being, even with a normal rate of respiration, far in excess of that required for saturation of the hæmoglobin in the pulmonary blood, we cannot believe that the increased frequency of respiration is called forth by a deficient oxygenation of the pulmonary blood; and it is impossible, for many reasons, to imagine that it is directed to a hyper-oxygenation of the pulmonary blood by increasing the tension of oxygen in the blood-plasma. Moreover, we have no reason to think that a smaller amount of blood than normal is passing through the lungs in a given time, especially as the rate of heart-beat is increased to a disproportionate extent. It is, therefore, very difficult to regard the tachypnœa as compensatory.

The true explanation seems to lie in the nervous relationships of the heart and lung functions. Both heart and lungs are supplied by the vagus, and the respiratory and cardio-inhibitory centres are in close anatomical and physiological relationship with one another. Both centres are normally dependent upon the degree of aëration of the blood, both are readily affected by afferent impulses reaching them from distant parts of the body. Though independent of one another in a sense, they are very liable in ordinary life to be called into play simultaneously, and the alteration in rate of action that is commonly called for is in the same direction in both organs, whether it be quickening, as during muscular exercise, or slowing, as during rest. This is well shown by the remarkable constancy with which the normal ratio between rate of heart-beat and rate of respiration (3–4 : 1) is maintained in health, and the few diseases in which it is disturbed.

This being the case, it is probable that the tachypnœa of early cardiac disease is an associated rather than a compensatory change. Normally, when the rate of heart-beat is increased, the rate of respiration is increased also, because both conditions are required. A contracting system of muscles, for example, requires a greater amount of blood, and forms a greater amount of carbonic acid; therefore the heart must beat more rapidly and more forcibly to supply the muscles and to carry the vitiated blood to the lungs, and the lungs must be inflated more often, otherwise the more rapid flow of blood through them would mean its deficient oxygenation. But the nervous system, by which these associated changes are regulated, is not able to distinguish between the rapid action of a normal healthy heart and the rapid action of a diseased heart, and therefore it throws into play the respiratory centre, and increases the rate of respiration whenever the diseased heart acts rapidly. And since, owing to purely cardiac causes, this is of frequent occurrence, shortness of breath becomes one of the most constant symptoms of cardiac disease. But the symptom is associated, not compensatory.

In late cardiac disease the case is different. Here we have not only tachypnœa, but also definite dyspnœa. Here, too, the rate of heart action is by no means always increased, often it is diminished. But whether the rate of beat is increased or diminished, the force of individual beats is always less than normal owing to failure of the right ventricle, and the lungs are engorged with blood. Hence, in late cardiac disease there is no doubt that the velocity of blood-flow through the lungs is greatly diminished. The lungs, too, are œdematous, and the available area for oxygenation of blood is diminished also, for the alveoli are partly filled with fluid. Therefore, in late cardiac disease, when the heart is failing, the increased rate of respiration is not associated as it is in early disease; but, as the cyanosis shows, it is compensatory, and due to a deficient aëration of the blood. It is as distinctly an equilibrating disorder of respiration as is the dyspnœa occurring in stenosis of the larynx.

François-Franck investigated the subject of cardiac dyspnœa from the experimental side. He found that every abnormal irritation of the aorta or heart may provoke reflex respiratory phenomena. These may be spasmodic, or inhibitory, or acceleratory, according to the kind of irritation. They are often accompanied by spasm of larynx, bronchi, or pulmonary vessels if the dyspnœa is of medium severity; if the dyspnœa is very slight and respiration is quickened, or if there is complete arrest of respiration, spasm of bronchi or of pulmonary vessels does not occur. According to this author, therefore, the dyspnœa of late cardiac disease has marked analogies with spasmodic asthma. The only effect of a valve lesion appears, from his experiments, to be an intensification of phenomena which can well be called forth in the absence of a valve lesion.

(ii.) **Renal Dyspnœa.**—Renal dyspnœa is even more complicated in its pathology than cardiac dyspnœa. In some cases it may be essentially a dyspnœa of late cardiac disease, for it has repeatedly been stated, in the preceding pages, that the later symptoms in renal disease of the fibrotic variety are often purely cardiac. But in uræmia there is frequently a dyspnœa which is not of cardiac origin. This variety of dyspnœa has distinctly more resemblance to spasmodic asthma than the dyspnœa observed in cardiac disease. Thus, it is often paroxysmal, and sometimes especially affects expiration. In most cases of uræmia, however, there is a hissing tachypnœa, in which the rate of respiration is markedly increased without any particular modification of either inspiration or expiration. As to the pathology of uræmic dyspnœa, we are very uncertain. We are bound to conclude that it depends upon an altered constitution of the blood, and it is probable, bearing in mind the frequent occurrence of epileptiform convulsions in uræmia, that it is brought about by action of the altered blood upon nervous centres, but more than this cannot be said at present. In particular, it is unknown how far it may depend upon alterations in the lungs, whether œdema similar to that which sometimes affects the larynx in acute renal disease, or muscular spasm similar to that which is regarded as being the cause of spasmodic asthma.

(iii.) **Heat Dyspnœa.**—Heat dyspnœa, properly so called, is a phenomenon which is seen to a marked extent in animals that have been exposed to high external temperatures. There is some uncertainty with regard to its pathology, though there is no doubt that the increased frequency of respiration has for its object an increased heat loss. Most authors maintain that it depends upon the fact that over-heated blood reaches the respiratory or thermic centres, but Sihler maintains that increased warmth of the skin, and not increased warmth of the blood, is the effective factor. Thus he found that whereas an animal with severed spinal cord, and therefore with poor cutaneous circulation, when exposed to external warmth, suffered a rise of 1° C. in body temperature, and increased his respiration by 25 per cent., a normal animal, exposed in the same way to external warmth, increased his rate of respiration by 800 per cent., though at the same time his body temperature did not rise at all. The accelerated respiration of hyperthermia is essentially a heat dyspnœa, and probably the increased frequency of respiration in fever is of the same nature; but on this point we cannot be so certain, owing to the presence of toxic substances in the blood in febrile diseases. Reference has already been made (p. 452) to the effects of supplying the brain and spinal cord with experimentally heated blood.

**IV. Respiratory Modifications due to Morbid Conditions of the Blood.**—Though, of course, pathological modifications of respiration fundamentally depend upon a deficient aëration of the blood (using the expression in the broadest possible sense), it is only when some morbid condition of the red corpuscles is present that the blood itself can be primarily inculpated; hence, as a matter of fact, morbid conditions primarily affecting the blood form a minority amongst the causes of disordered respiration, if we may eliminate from this category the respiratory changes in febrile conditions. With this exception, all primary morbid conditions of the blood leading to disordered respiration act by way of anæmia.

The respiratory modifications seen in anæmic conditions, when the patient is at rest, are not, as a rule, dyspnœic. Respiration may be slightly increased in frequency, but the principal effect of the anæmia is a tachypnœa on exertion, and this may undoubtedly be distressful. Nevertheless, in extreme cases of anæmia, such, for example, as that seen after profuse hæmorrhage, the "air-hunger" may be intense, and the respirations panting. If, however, the patient is moribund, respirations are likely to be infrequent and sighing in character.

The pathology of breathlessness in anæmia having been considered elsewhere (p. 178), it is unnecessary to advert to the question here.

**V. The Effects of Abnormality of the Respired Air.**—The alterations that may be undergone by the air presented for respiration are innumerable, for they include all conditions from respiration of rarefied air to respiration of abnormal gases, such as nitrous oxide, chloroform-vapour, ether-vapour, etc., administered in order to produce anæsthesia. There is, therefore, no limit to the length at which this section might be discussed. Nevertheless, the chief pathological effects of alterations in the respired air are due to a deficient oxygenation of the blood, aided, in some cases, by the direct effects of some constituent gas having irritating or poisonous properties.

(i.) **Deficiency of Oxygen.**—The effects of gradually diminishing the amount of oxygen in air do not become manifest until the amount of oxygen present has been reduced from the normal 21 per cent. to about 12 per cent.. and even then the only symptom recognisable is a slight increase in depth of respiration. "At 10 per cent. the respirations are distinctly deeper and more frequent and the lips become slightly bluish. At 8 per cent. the face begins to assume a leaden colour, though the distress is still not great. With 5 or 6 per cent. there is marked panting, and this is accompanied by clouding of the senses and loss of power over the limbs, which would probably end sooner or later in death. . . . . When air containing less than 1 or 2 per cent. of oxygen is breathed, loss of consciousness, without any distinct previous warning symptom, occurs within about forty or fifty seconds. . . . . Loss of consciousness is quickly succeeded by convulsions, which are followed by cessation of the respirations. The heart still continues to beat, in the case of cats and dogs, for from two to eight minutes."[1]

The pathological conditions in man with which these experimental reductions in the amount of oxygen in the air may be compared, are (*a*) "mountain-sickness," and the symptoms often observed by aëronauts, (*b*) the effect of inhaling carbon monoxide ("after-damp"), which Haldane's investigations have shown to be the principal cause of death in colliery explosions.

In all these cases, though there are great differences in the manner of its production, the final result is the same, and consists in a deficient oxygenation of the blood, using that term in a broad sense.

(*a*) *Mountain-sickness.*—Mountain-sickness has at different times been ascribed to different causes, of which the chief—heart-failure, fatigue, indigestion, diminished barometric pressure, deprivation of oxygen—are fully discussed by Allbutt in his *System of Medicine.* In this article Allbutt expresses his adhesion to the view that deprivation of oxygen is the essential factor, though he points out that the other alleged causes undoubtedly play an important part in determining the particular altitude at which the disorder shall show itself. The highest altitude that has been attained without symptoms of mountain-sickness is 16,500 feet. At this altitude the oxygen tension in the atmosphere corresponds to an oxygen tension of about 10 per cent. at sea level, so that there is a remarkable agreement between practical experience in mountaineering and the result of diminishing the amount of oxygen in the air used for respiration by direct experiment, as described above. Haldane and Lorrain Smith bring forward evidence to show that the symptoms caused by diminution in the oxygen tension of the air breathed are due to a fall in the oxygen tension reached by the blood in the lungs, and not to diminution in the quantity of oxygen carried by the blood from the lungs. They find that in birds and mice, under pressures of one-third to one-quarter of an atmosphere, the oxygen tension in the arterial blood leaving the lung, though lower than normal, is still high enough to saturate the hæmoglobin almost completely, even when the animal is at the point of death.[1]

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[1] Haldane's Report to the Secretary of State for the Home Department on the "Causes of Death in Colliery Explosions, 1896," p. 15.

(*b*) *Poisoning with Carbon Monoxide.*—Inhalation of carbon monoxide produces symptoms which are in many respects similar to those of mountain-sickness. Thus the principal symptoms consist in dizziness, weakness of the legs, dimness of sight, palpitation following any extra exertion; as in mountain-sickness, severe headache, nausea and vomiting also occur, though they are seen especially in patients recovering after a more or less lengthened exposure to the gas. Gradual inhalation of the gas, as when the amount present is not great (·1–·2 per cent.), is accompanied by very little actual distress, owing to the insidious manner in which carbon monoxide produces its effects. Haldane has pointed out that in colliery explosions the position of the bodies gives evidence that death has been peaceful.

Carbon monoxide produces its effects, owing to the fact that its affinity for hæmoglobin is about 250 times as great as that of oxygen for hæmoglobin. When, therefore, the blood is exposed to a mixture of these two gases, carboxyhæmoglobin is formed until the tension of carbon monoxide in the blood corresponds with the tension of the gas in the atmosphere. Air containing ·1 per cent. of carbon monoxide causes the blood to become about half saturated with this gas. Since carboxyhæmoglobin is useless for respiratory purposes, the final result of respiring air containing this percentage of carbonic monoxide is the same as if the oxygen tension of the air breathed had been reduced by half. In the case of colliery explosions, the greatest percentage saturation of the victims' blood with carbon monoxide found by Haldane was about 80 per cent.

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[1] "Caisson" disease, which occurs in those who have been exposed to increased barometric pressure of air (*e.g.*, persons engaged in tunnelling operations), and manifests itself when they again become exposed to atmospheric pressure, is, according to Snell, rather due to insufficient ventilation than to decompression. But there are certain points concerned with its incidence which are difficult to explain on this supposition. Especially so is the fact that "caisson" disease shows a much greater liability to affect persons above the age of 45 years than those below the age of 25 years. (Snell, *Compressed Air Illness or so-called "Caisson" Disease*, 1896.)

(ii.) **Increase of Carbon Dioxide.**—Inhalation of carbonic acid gas has well-marked effects upon respiration. In a series of careful experiments, Haldane and Lorrain Smith found that it causes no appreciable symptoms until it constitutes 3–4 per cent. of the inspired atmosphere, but at that point it causes a slight deepening of respiration; 6 per cent. causes panting and some headache; with 7–8 per cent. panting is very distressing, and with 10–11 per cent. respiratory distress is extreme; higher percentages seem to have an anæsthetic effect. The gas does not act only by diluting the oxygen, but is distinctly poisonous, for the symptoms mentioned are seen when the normal percentage of oxygen in the air is fully maintained, and even when it is definitely increased.

In connection with increase of carbonic acid in an atmosphere we must briefly consider the effects of breathing air that has already been used for respiration.

There is no doubt that breathing air which has been repeatedly used for respiration causes a considerable discomfort, which shows itself principally by increased frequency of respiration and by frontal headache. Further, the historic instance of the Black Hole of Calcutta is ample evidence that repeated respiration of the same air is highly dangerous to life.

It is certain that other substances besides carbonic acid (exhalations from the bodies of individuals, etc.) collect in a badly ventilated room in which persons are congregated, and to these, as well as to the carbonic acid itself, Haldane and Lorrain Smith ascribe the frontal headache; the increased frequency of respiration they ascribe almost entirely to the carbonic acid alone. But they maintain that the air of the closest dwelling-room—though a source of discomfort—is not an immediate source of danger to life. For they found that the amount of carbonic acid that can be borne without discomfort (much less, danger) by breathing respired air from which *smell* is absent, is ten to twenty times as great as the amount present in the worst ventilated living-room.

With regard to the cause of immediate danger in repeated respiration of the same air, there are two distinct views: (1) that of Hermans and of Haldane and Lorrain Smith, who believe that the danger lies solely in excess of carbonic acid and deficiency of oxygen; (2) that of Brown-Séquard and D'Arsonval, who maintain that the danger is due to the presence of some toxic substance of undefined nature, but other than carbonic acid, in air that has been used for respiration.

Brown-Séquard and D'Arsonval concluded from a series of experiments that respiration adds to air a toxic substance other than carbonic acid, which is a direct menace to life. They kept rabbits in an atmosphere which was constantly renewed, but which consisted of air that had been respired by other rabbits. The animals almost invariably died after a longer or shorter time, whereas animals which breathed the same air, after it had been passed through sulphuric acid, survived. They concluded that expired carbonic acid has no part in the poisonous quality of respired air.

These experiments, however, are not fully convincing. For an undiscovered leak through which fresh air reached the animals that survived, and owing to which they did not receive the same amount of previously respired air as the animals that died, would explain the whole experiment from the points of view of Haldane and Lorrain Smith. And even if this possibility were excluded, there is no evidence that it was the products of respiration that killed certain of the rabbits, rather than accidental putrefactive and other gaseous products, such as are present in all cages in which animals are confined. Moreover, several authors have repeated the various experiments of Brown-Séquard and D'Arsonval, but have failed to obtain similar results. It is, therefore, safer to conclude at present that the danger of breathing air that has been repeatedly used for respiration lies, not in the fact that it contains some specific poison, but in its excess of carbonic acid and its deficiency of oxygen.

It is important in this connection to note that symptoms are more readily called forth by increase of carbonic acid in the air breathed than by a diminution of oxygen; 3–4 per cent. increase of carbonic acid produces the same effects upon respiration as about 9 per cent. diminution of oxygen. It follows, from all that has gone before, that excess of carbonic acid causes panting long before there is serious danger to the individual, diminution of oxygen hardly gives any warning until danger is imminent.

(iii.) **Presence of Abnormal Gaseous Constituents.**—Into the respiratory disorders produced by inhalation of gases such as ammonia, sulphur dioxide, sulphuretted and arseniuretted hydrogen, etc., we shall not enter here. In some instances they reduce oxyhæmoglobin (*e.g.*, $H_2S$); in others they act by their direct poisonous effects, and then often produce symptoms less marked in the case of respiration than in the case of other functions (*e.g.*, $H_3As$); in other instances they act by their pungent characters and produce spasm of the glottis (*e.g.*, $NH_3$); in yet others they act by the production of bronchitis and bronchopneumonia. Upon the subject of chloroform- and ether-inhalation, however, a few words must be said.

*Chloroform-inhalation.*—The chief point of discussion in this highly controversial subject is whether death from chloroform depends upon failure of respiration, as is held by Lawrie and the Hyderabad Commissioners, or whether it depends upon cardiac paralysis and dilatation, as is held by most investigators, amongst whom MacWilliam, Ringer, Hare and Thornton, Gaskell and Shore, and Hill must be mentioned.[1] Since there is a general accord that, in death from chloroform, respiration fails first, the real point at issue resolves itself into the question whether chloroform has, or has not, a direct effect upon the heart. Subordinate questions, as, for example, whether chloroform leads to vaso-motor paralysis, are subjects of discussion even amongst those who maintain that the heart is itself affected.

In my opinion, the question, whether chloroform, administered as in chloroform-anæsthesia, has a direct action upon the heart, was conclusively answered in the affirmative by the cross-circulation experiments of Gaskell and Shore. By an ingenious but complicated method of making artificial communication between the arteries and the veins of two animals, Gaskell and Shore were able, by giving chloroform to one animal or the other of the pair, to determine that the chloroform-bearing blood should supply either the heart or the brain, exclusive of the other organ. Under these circumstances they found that the blood-pressure falls rapidly when the heart is directly supplied with chloroform-bearing blood. To these experiments Lawrie objects, though, in the opinion of most observers, on insufficient grounds.

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[1] Those specially interested in the subject should read the report of a discussion (held at the Royal Medical and Chirurgical Society and published in the Society's *Transactions* for 1895), in which Lawrie, Gaskell, Shore, Lauder Brunton, and others took part; also the Report of a Discussion on Anæsthetics at the Montreal meeting of the British Medical Association (reported *Brit. Med. Journ.*, 1897, vol. ii.).

Hill has applied his work upon the effects of gravity on the circulation to the question. He has shown that with moderate anæsthesia the "feet-down" position produces a slight fall in blood-pressure, which can be restored to the normal height by compression of the abdomen. When chloroform-anæsthesia is pushed, however, a very great fall of blood-pressure takes place for which compensation cannot be made by compression of the abdomen, or even by the "feet-up" position. The fall of blood-pressure in the latter case is therefore different from that in the former. Since blood-pressure depends upon the two factors, peripheral resistance and output of the heart, and the effects due to peripheral dilatation (especially in the splanchnic area) are neutralised by compression of the abdomen, it follows that the fall of blood-pressure with deep anæsthesia depends upon the cardiac factor. By quite a different method, therefore, Hill corroborates the other authors who maintain that chloroform has a direct action upon the heart.

Death from chloroform occurs under two different conditions: (1) It occurs quite early in anæsthesia, often long before the surgeon has begun to operate; (2) it occurs in deep anæsthesia when the patient has been unconscious for some time. The explanation of the result under these two different conditions is probably the same, and depends upon paralytic dilatation of the heart, but the immediate methods whereby the result is brought about seem to be somewhat different. The first effect of administering chloroform to a conscious individual, especially if the amount of chloroform on the inhaler is very large, is struggling and an arrest of respiration; this leads, of course, to distension and dilatation of the right ventricle. At last the need for respiration becomes imperative, and deep inspirations are taken, by means of which the pulmonary blood becomes suddenly exposed to air containing a large amount of chloroform. The blood, therefore, becomes highly charged with the drug, and is, in that condition, conveyed to the myocardium by way of the coronary arteries. After a short period of rapid heart-beats, which quickly become feeble, the heart entirely fails to contract. In these cases, according to Hill, respiration and pulse cease simultaneously, or the pulse ceases first. Death, during deep and prolonged anæsthesia with chloroform, is probably brought about in the same way, excepting that respiration fails first, because the great fall in blood-pressure produces an anæmic exhaustion of the respiratory centre which is coupled with its narcotisation. In the first class of case it is easy to understand that artificial respiration almost always proves ineffectual; in the second class, Hill maintains that artificial respiration, if adopted in time, will always resuscitate the patient.

*Ether-inhalation.*—Ether, according to Hill, has quite a different effect from chloroform. Even when the blood-pressure falls considerably, as it does when administration of the drug is pushed, compression of the abdomen is always sufficient to restore the blood-pressure to its original height. In the case of ether, therefore, it would seem that the heart is unaffected. Though it may be conceded that the effects of ether on the heart are far less than those of chloroform, I have seen numerous unpublished tracings taken by Roy directly from the ventricle, and these certainly do not substantiate the view that ether is without effect upon the heart, but yield evidence in exactly the opposite direction. These tracings showed that ether dilates and paralyses the heart like chloroform, though much less readily.

VI. **Asphyxia, Dyspnœa, and Orthopnœa.**—The changes occurring in asphyxia, dyspnœa, and orthopnœa differ from one another in degree rather than in kind; it will, therefore, suffice to discuss asphyxia and indicate subsequently the differences which obtain between it and the two other conditions. Certain points in connection with orthopnœa, however, will need special discussion.

*Asphyxia.*—The effects of asphyxia are seen over the whole body, but interest centres chiefly in the behaviour of the respiratory and the vascular systems; these will be discussed separately, but very briefly, because of the attention bestowed on the subject in physiological works.

When the trachea of a normal animal is suddenly occluded, the length of time that elapses before respiratory movements show that the animal is in need of air, though it does not extend beyond twenty or thirty seconds at most, varies according as occlusion has been made at the end of an expiration or of an inspiration. Under any circumstances, however, the period of quietude gives place to respiratory movements, both of inspiration and expiration, which increase in frequency and in force until, at the end of about one minute from the time when the trachea was occluded, the animal is powerfully convulsed. At this time respiratory movements are chiefly of the expiratory type, but gradually a period of exhaustion sets in, and the character of respiration changes from a mainly expiratory to a mainly inspiratory type, while the rate of respiration diminishes. Each respiratory effort, however, is accompanied by contraction of all the accessory muscles, and the efforts themselves are prolonged. From early in the second minute, the animal is unconscious; his sphincters are relaxed, and involuntary passage of urine and fæces is usual, owing to participation of the unstriped muscle of bladder and intestine in the general contraction of muscle throughout the body.

Of the vascular results of asphyxia, the acute dilatation of the heart and the consequent cardiac failure have already been mentioned at sufficient length (p. 77); here we shall only consider the blood-vessels. To observe the vascular changes uncomplicated by respiratory effects it is necessary to use a curarised animal.

If, in a curarised dog or rabbit, while a graphic record is being taken of the general blood-pressure, artificial respiration is suddenly suspended, during the asphyxia which follows (but which is, of course, unattended by muscular movements), the following changes are noted. The blood-pressure begins to rise almost immediately, and rises steadily and rapidly until it has reached a point far above the normal. During the earliest portion of the rise the excursions corresponding to the heart-beats are somewhat quickened, but very soon they become slower than normal, and much more forcible. After the blood-pressure has reached its maximum it begins to fall, rapidly at first, but more gradually after it has repassed the normal and approximates to zero. During the early part of the fall, the tracing shows that heart-beats are still forcible and infrequent, but soon this gives place to an increased rapidity with diminished force, which in its turn is followed by an infrequency and generally an irregularity of beat with still further diminished force. By this time the animal is very near death, but, as a rule, re-establishment of artificial respiration is sufficient to bring about a rapid recovery of blood-pressure, however low it has fallen, so long as the heart has not actually ceased to beat. During some portion of the whole curve given by the blood-pressure in asphyxia—roughly speaking, over the middle three-fifths—the rhythmic Traube-Hering curves are observable.

In an animal that is not under the influence of curare the blood-pressure curve in asphyxia is modified by the effect of the respiratory movements, but the rise of pressure seen under normal circumstances with inspiration is, in asphyxia, replaced by a fall.

The venous blood-pressure during asphyxia rises enormously under any circumstances, but the rapidity with which the rise occurs is greater in a non-curarised animal owing to the powerful effect produced by the convulsive movements upon the venous blood-flow.

In the production of these changes—respiratory, cardiac, and vascular—it is a little difficult to decide the relative importances of the excess of carbonic acid and of the deficiency of oxygen which result from asphyxia. There can be no doubt, however, that the early respiratory distress and the violent respiratory movements are essentially due to over-charging of the blood with carbonic acid; but the fact that whereas ordinary venous blood still yields the spectroscopic bands of oxyhæmoglobin the blood in asphyxia does not, shows that, in the later stages of suffocation, deficiency of oxygen must play a highly important part. And yet there is really no change from beginning to end that cannot be explained as the result of a definite poisoning by carbonic acid. Over-charging of the blood with carbonic acid leads to respiratory distress, because venous blood is one of the most potent stimuli to activity of the respiratory centre; it leads to a rise of blood-pressure because it induces vaso-constriction throughout the body (but especially in the splanchnic area) by stimulating the vaso-motor centre; it causes the early slowing and strengthening of the heart-beat by stimulating the cardio-inhibitory centre, and the later increased frequency with feebleness of beat by paralysing the cardio-inhibitory centre and impairing the contractile power of the cardiac muscle; it causes unconsciousness by the anæsthetic effects which it produces when in a high degree of concentration. The most that can be directly ascribed to deficiency of oxygen is a part share in causing the unconsciousness, the panting, and the convulsions; but even here deficiency of oxygen simply takes up and carries on a work that has already been commenced by excess of carbonic acid. And yet, in the actual production of the fatal event, we cannot but believe that deficiency of oxygen is as important as excess of carbonic acid.[1]

*Dyspnœa.*—Dyspnœa is really nothing more than a prolonged and sub-acute form of asphyxia, and as a result the respiratory and vascular changes are similar to those of asphyxia, though they run a less stormy course. In the case of vascular changes, it is only necessary to diminish the supply of air to a curarised animal, instead of completely suspending artificial respiration, for the similarity of the changes in dyspnœa and in asphyxia to become evident; the rise of arterial and venous blood-pressures, the evidence of vagus action on the heart, the Traube-Hering curves, the final fall in arterial blood-pressure, appear as in asphyxia, though it may take hours to produce the same differences as, in asphyxia, are produced in minutes or less.

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[1] In the case of curarised dogs, I have found in some hitherto unpublished experiments, that, after intra-vascular injection of diphtheria toxin, suspension of artificial respiration frequently does not lead to a rise of blood-pressure, though the effects of vagus action are generally seen. This would seem to indicate that diphtheria toxin has some special effect in these cases upon the vaso-motor centre, or upon the muscular walls of arterioles. The observation is of interest in view of the fact that laryngeal diphtheria leads to a dyspnœa frequently amounting almost to asphyxia. If, as is probable, we are to regard the rise of blood-pressure in asphyxia as being protective in nature it would appear that diphtheria not only tends to produce asphyxia, but also tends to abolish one of the protective means whereby certain of its ill-effects are minimised.

In a period of very moderate, and therefore very prolonged, dyspnœa, the initial rise of arterial blood-pressure may not be seen, owing to the fact that $CO_2$ does not accumulate in the blood in sufficient quantity to lead to a general vaso-constriction of the splanchnic area. In such cases the blood-pressure curve is maintained at a normal level for a long time. But the insufficient aëration of the blood, aided by other causes, impairs the efficiency of the cardiac muscle, so that ultimately the blood-pressure falls as in more acute cases, and once it has begun to fall, it continues to do so far more rapidly than might at first be expected. The degree of dyspnœa has a marked effect upon the duration and the height of the rise of blood-pressure, but far less effect upon the length of time it takes for the blood-pressure to fall to zero, once the fall has commenced.

So far as cardiac changes are concerned, the ventricular dilatation seen in asphyxia also occurs in dyspnœa, though to a less marked extent. The processes, however, whereby the dilatation is brought about in the two cases are probably different; this question has already been sufficiently discussed along with the Pathology of the Heart (pp. 75–78). The respiratory changes of dyspnœa may involve both inspiration and expiration to a nearly equal extent, but the differences between the modes of respiration in bilateral paralysis of the posterior crico-arytenoid muscles, and in emphysema, show that dyspnœa may be either principally of an inspiratory, or principally of an expiratory type. Reference has already been made to the change in type of respiration during the later stages of asphyxia. Respiration is almost invariably quickened in dyspnœa, and often to a very considerable extent; thirty to forty respirations per minute is a very common rate.

*Orthopnœa.*[1]—In many cases of dyspnœa, respiratory distress is so much greater when the patient is lying down than when he is sitting up, that he adopts the latter position; dyspnœa of this description is usually described under the special name of "orthopnœa." The position adopted by the patient varies in different cases, so that the term is not etymologically applicable to all the conditions to which it is commonly applied. His dyspnœa varies from a condition in which complete relief is given by placing an additional pillow beneath his shoulders, to conditions in which he finds maximum relief—but is still intensely dyspnœic—when sitting perfectly upright, or even leaning somewhat forward. It is convenient to divide orthopnœa into "partial" and "complete," according as the angle formed by the patient's back with the horizontal plane is less than or greater than 45°.

Orthopnœa may show itself with dyspnœa arising from any cause, *e.g.*, cardiac disease, renal disease, emphysema, spasmodic asthma, pleural, pericardial, and peritoneal effusions, pulmonary embolism, acute bronchiolitis, pneumothorax, aneurysm of the aortic arch, angina pectoris, etc. Mere tachypnœa without respiratory distress is generally unaccompanied by orthopnœa, thus patients suffering from croupous pneumonia or widely disseminated pulmonary tuberculosis are rarely orthopnœic. Perhaps owing to the relative prevalence of aortic valvular disease in men, and the frequency with which aortic regurgitation is associated with orthopnœa, the condition is more commonly seen in men than in women.

The following are striking clinical points in connection with orthopnœa:—(1) The onset of orthopnœa is, in the large majority of cases, quite sudden,[1] the patient being forced to sit upright owing to the sudden supervention of a sensation of impending suffocation. (2) Most cases of orthopnœa are complete from the very first.[2] (3) Once a patient has become in any degree orthopnœic, the condition frequently advances, but rarely recedes;[3] it follows from this, that though partial orthopnœa may become (and often does become) complete, it is very uncommon for complete orthopnœa to become partial. To this statement spasmodic asthma, when uncomplicated by permanent and advanced changes in the right ventricle, offers an exception, for though the patient is completely orthopnœic during attacks, in the intervals he is commonly able to adopt a normal horizontal position when in bed. (4) Speaking generally, the angle with the horizontal plane assumed by the patient approximates more to a right angle as the degree of dyspnœa is greater. Hence follows the corollary, that, as a general rule, patients in whom the orthopnœa is partial, suffer no respiratory distress (though they may still be tachypnœic) when resting at the particular angle which they assume; for if at this particular angle they experienced distress, they would assume a more nearly perpendicular position. In the case of complete orthopnœa there may not be respiratory distress, but usually distress is great.

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[1] So far as I have been able to discover, the pathology of orthopnœa has never been systematically investigated. In 1892 I made notes of fifty-six cases (male and female), and since that time have followed the histories of the patients as far as possible. These observations, which are hitherto unpublished, were made in the wards of St George's Hospital, and it is upon them that I base the remarks made in the text. I take here the opportunity of thanking the physicians in charge of the cases for ample facilities in examining the patients and their records, both during life and after death.

The pathology of orthopnœa is greatly obscured by the fact that, in the majority of cases, both heart and lungs are involved, so that it becomes difficult to decide whether the dyspnœa is primarily of cardiac or primarily of pulmonary origin. It is my opinion that, in the large majority of cases, the actual onset of orthopnœa is accompanied by a sudden dilatation of the right ventricle, whether that depends upon antecedent pulmonary conditions or no. In favour of this view are the observations that the onset of orthopnœa is markedly sudden, and that in nearly 80 per cent. of my cases in which an autopsy was made (twenty-two cases), the right ventricle was found greatly dilated, while in a similar percentage of cases examined only during life, cardiac dulness was extended to the right of its normal limits.

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[1] In my cases the proportion of those with sudden onset to those with gradual onset was 7 : 1.

[2] In my cases the proportion of those beginning as complete to those beginning as partial was 2 : 1.

[3] In only five of my cases did an orthopnœa recede.

But, as might be expected, it is exactly in patients with dilatation of the right ventricle that one meets with œdema of the lungs, hydrothorax, pulmonary collapse, etc., and it is impossible to decide the extent to which these conditions are responsible for the orthopnœa. Nevertheless, cases of pulmonary embolism are extremely important in this connection, for in them the cardiac condition is clearly one of acute dilatation of the right ventricle, and there is no question that the orthopnœa is of cardiac and not of pulmonary origin. In the opposite direction croupous pneumonia is equally important, for here there is no orthopnœa, and the right heart is not acutely dilated.

But though I think that orthopnœa is *generally* an indication of a sudden dilatation of the right ventricle, some cases are certainly not susceptible of this explanation. For in a small percentage of cases, evidence of cardiac enlargement is completely wanting. It appears certain, however, that for the occurrence of orthopnœa, cardiac action must, in some way or other, be impeded; pulmonary and other diseases, in which the heart is not involved secondarily and considerably, are not accompanied by orthopnœa.

Perhaps the most curious feature of orthopnœa is the posture itself. In all diseases accompanied by pain or distress, excepting those leading to orthopnœa, the patient commonly experiences most relief when lying down, and sitting up is a sign of convalescence. But here the exact converse is the case. That the orthopnœic patient sits up because he experiences most relief in that position is a truism, but it is not quite easy to determine how this position gives him relief. Probably it does so, in part, by lessening upward pressure of the abdominal viscera on the diaphragm, in part, because the action of gravity on the circulation, as pointed out by Hill, tends in the "feet-down" position to empty the heart, and therefore to relieve cardiac distension, and in part, because the shoulders are thrown back when taking a deep inspiration, and this action is less impeded in the upright position than in the horizontal position. Unfortunately, however, one has to confess that the pathology of orthopnœa is still almost a mystery.

VII. **Cheyne-Stokes Respiration.**—The peculiar respiratory modification, known by the names of Cheyne and Stokes, consists in a periodic waxing and waning of respiration. The cycle commences with infrequent and almost imperceptible respirations, which gradually become deeper and more rapid, until there is produced a condition of positive dyspnœa with very hurried and deep breathing; this, in its turn, gradually gives place to shallow and infrequent movements, ending in a complete pause. The duration of the ascending and descending phases is about the same, and the whole cycle is repeated about three times a minute.

Under pathological conditions, Cheyne-Stokes breathing may show itself in almost any disease of severity, but it is perhaps most commonly associated with diseases of the kidney. In adults it is always a grave sign, though it is not invariably a precursor of death; in children, its prognostic importance is far less. The rhythm may show itself several days before death in fatal cases.

It is impossible to discuss the pathology of Cheyne-Stokes respiration at any length, but it is necessary to remember that the respiratory phenomenon is only the most prominent of a whole series of periodic phenomena which may show themselves at the same time in the same patient, and are undoubtedly closely allied. The other phenomena to which reference is made, are periodic variations, in the size of the pupils, in size of the pulse, in blood-pressure, and in consciousness. The true explanation of Cheyne-Stokes breathing must explain these phenomena also.

At the outset, it may be said that no fully satisfactory explanation of Cheyne-Stokes breathing, and the other periodic phenomena that may accompany it, has been given. Gibson, whose admirable monograph on the subject is the latest and fullest, divides the explanations that have been given into three groups:

(1) earlier and vague explanations, (2) those which regarded the phenomenon as dependent upon variations in extrinsic stimuli received by the respiratory centre, (3) those which regard the phenomenon as dependent upon the intrinsic nutritive condition of the respiratory centre.

The first group needs no discussion. The earliest attempt at an explanation of the second kind was that of Little, who suggested that the two sides of the heart do not contract simultaneously or with equal force, and that the left ventricle is the more affected; as a result he supposed that the blood received by the bulb varied periodically in its degree of oxygenation.

Little's theory was followed by the renowned theory of Traube, who considered that the respiratory centre may be stimulated in two ways: (1) by way of the terminations of the vagus in the pulmonary blood-vessels, which are readily stimulated, are normally bathed with venous blood, and produce shallow respirations; (2) by way of the ordinary afferent nerves of the body, which are not normally bathed by venous blood, but which, when they are so bathed, cause dyspnœic respirations. He therefore explained the Cheyne-Stokes rhythm by supposing that the early and late respirations of the cycle are called forth by way of the pneumogastric nerve, the dyspnœic respirations of the middle of the cycle called forth by way of the ordinary nerves of the body. That the latter nerves played any part at all, he ascribed to a lessened irritability of the respiratory centre, which depended upon the cardiac or other change underlying the whole phenomenon, and owing to which a greater amount of $CO_2$ than normal accumulated in the blood before it sufficed to call forth respiratory movements at all. The pause he ascribed to a temporary hyper-oxygenation of the blood as the result of the dyspnœic respiration. This ingenious hypothesis Traube subsequently modified as the result of Filehne's criticism, and ultimately he ascribed the phenomenon to a rhythmic periodicity of the respiratory centre and its exhaustion during the phase of dyspnœic breathing. This modified explanation is, however, unsatisfactory in that it does not account for the early or ascending portion of the cycle, and gives no valid reason for commencement of the periodicity itself.

Filehne's hypothesis, which, in its original or in a modified form, has claimed as many adherents as that of Traube, was that, in health, venous blood excites first the respiratory centre, then the vaso-motor centre, and last of all the convulsive centres. He supposed that in cases where the Cheyne-Stokes breathing is present, the irritability of the respiratory centre is lessened, so that it fails to respond as normal to a venosity of the blood; this accounts for the pause in respiration. But the amount of $CO_2$ in the blood increases until it calls forth activity of the vaso-motor centre, which causes vaso-constriction and diminishes the amount of blood received by the respiratory centre to so great an extent that now the combined stimulus is sufficient to call forth respiratory movements. The blood, however, which is arterialised by these respirations, does not reach the respiratory and vaso-motor centres for some time, and in the interval the venosity of the blood generally has increased to such an extent that it calls forth dyspnœic respirations even from the enfeebled respiratory centre. Not only is this explanation highly complicated, but also it rests on the insecure basis that it presupposes vaso-constriction as a preliminary to the respiratory phenomenon. There is ample evidence that this assumption is unjustifiable.

The third group into which Gibson divides the explanations of Cheyne-Stokes respiration is that which supposes that the phenomenon depends upon intrinsic and periodic changes in the respiratory centre itself. An opinion of this kind is the one generally held at the present day. Luciani noted that the beats of the frog's heart often show a periodic grouping, and he endeavoured to associate the cardiac and the respiratory phenomena; he regarded the different forms of rhythm constituting the Cheyne-Stokes phenomenon as due to automatic oscillations in excitability of the centre itself. Rosenbach's explanation was closely similar in that he regarded the periodic breathing as an expression of the alternation of activity and repose characteristic of all kinds of living matter.

But it is by no means certain that extrinsic stimuli can be disregarded. Marckwald, from a long series of investigations, has concluded that periodic breathing can only manifest itself when some of the higher brain tracts have ceased to exert their normal influence on the respiratory tract; this he showed by making sections of the medulla oblongata at different levels above the respiratory centre. In this connection the fact is important that periodic breathing is often seen during hibernation of lower animals, and after administration of chloral, morphia, ether, chloroform, etc. Gad has shown, by simultaneous tracings of arterial pressure and respiratory movements, that Traube-Hering curves go hand-in-hand with Cheyne-Stokes breathing. And Lombard, in a highly interesting series of experiments, has shown that, when volition is brought to bear upon a centre for muscular movement that is fatigued, the movements produced show a periodicity. He found that if the finger be voluntarily contracted, the excursions that it makes progressively become smaller and less frequent, until after a time, however great the effort of volition, no contraction occurs at all. If efforts are still made to bend the finger, contractions gradually reappear, become as forcible as at first (or even more forcible), gradually disappear, to again appear and carry on the same cycle. The similarity to the Cheyne-Stokes rhythm is therefore very great.

It appears, then, that when a nerve centre is fatigued, or when its vitality is lowered, its action tends to become periodic. Probably Cheyne-Stokes breathing is one amongst many examples of this statement, and it is important to note in this connection that Pembrey maintains that Cheyne-Stokes breathing is normal in hibernating animals during their winter sleep. But it is also probable that the whole explanation is not exclusively bound up with the nutritive condition of the respiratory centre alone; there are reasons for believing that modification of the extrinsic stimuli normally received by that centre, also play a part in causing the phenomenon.

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# CHAPTER XV.

## Appendix.

*Synopsis.*

- I. "Ptomaine Poisoning."
- II. Life under Aseptic Conditions.
- III. Fragmentation of the Heart.
- IV. Death from Certain Causes.
    - (i) From Extensive Superficial Burns.
    - (ii) By Drowning.
    - (iii) From Thirst.
    - (iv) By Lightning and by Electric Shock.

In the present chapter brief space is accorded to certain conditions of interest for which suitable places could not conveniently be made elsewhere.

I. **"Ptomaine-Poisoning."**—The class of case to which the name "ptomaine-poisoning" is given, is at the present time very ill-defined, but it has gained somewhat in precision during the past few years. Originally, as its name implies, the term was used to indicate conditions in which symptoms of poisoning supervened as the result of ingesting substances formed during putrefaction of cadavera. Selmi, and following him, Brieger, endeavoured to give it greater precision by studying the chemical constitutions and the physiological actions of the products of decomposition of proteids. As a result of this work many cadaveric amines and alkaloids were isolated, some of which were harmless, others intensely poisonous, and "ptomaine-poisoning" came to be looked upon as a special form of poisoning by chemical substances.

This view, however, was shown to be too narrow, for it was found, with the progress of bacteriology, that in some cases of ptomaine-poisoning, symptoms come on immediately, or very shortly after ingestion of the inculpated food, whereas in other cases there intervenes a distinct interval of 24–48 hours. Since in these latter cases special bacteria are often to be found in the article of diet and sometimes in the blood or excretions of the sick person, we must regard this form of "ptomaine-poisoning" as being due to a distinct infection, and the interval which elapses between ingestion of the food and appearance of the symptoms as a distinct "period of incubation."

Food-poisoning of the description now under discussion was therefore seen to be of two kinds: (1) that due to the action of a chemical substance formed during putrefaction outside the body; (2) that due to a definite infection by a pathogenetic micro-organism present in the putrefying food. To these, Sidney Martin —in deference to clinical usage—adds a third kind of "ptomaine-poisoning," viz., that due to absorption of poisonous substances formed during putrefaction of food in the intestine.

In cases where poisoning is due definitely to some chemical substance, the period which elapses between ingestion of the food and appearance of symptoms does not generally extend beyond two or three hours. But this does not seem to be an invariable rule even in the case of a chemical substance; sometimes symptoms do not supervene for twenty-four hours or more. Analogous examples are known in certain other directions. Thus, after injection of anti-diphtheritic serum, the sterility of which is undoubted, joint pains, urticarial rashes, etc., in those cases in which they occur, may not supervene until perhaps a week after the subcutaneous injection has been given. Concerning the "incubation period of chemical poisons," however, nothing is known at present, though it is obviously a subject of great importance.

In connection with ptomaine-poisoning many facts have been recorded, the explanation of which is very difficult. Thus it is not infrequently found that a given article of food has been a source of danger for only a limited period. A marked example of this kind is given by Brouardel in his work on *Death and Sudden Death*. Brouardel is inclined to associate the fact with the different stages of putrefaction, that is, with the question whether the putrefactive substances have been formed early, and by aërobic bacteria, or late, and by anaërobic bacteria. So also it is remarkable that ptomaine-poisoning is, in a very large majority of cases, associated with consumption of pig meat. Ballard suggests that this may depend upon the large amount of gelatine formed during the cooking of pig meat, and the especial suitability, therefore, of pig meat as a culture-medium for bacteria; this explanation Martin considers is highly probable. In the majority of cases, foods which cause ptomaine-poisoning are not obviously in a state of decomposition; as a rule, indeed, they are normal in appearance and in smell.

II. **Life under Aseptic Conditions.**—The question how far the myriads of bacteria inhabiting the intestinal tract of an individual are conducive to his welfare, became a subject of interest directly it was recognised that the actions of bacteria are not wholly detrimental, and that by their aid the complex proteid molecule is readily split up. The special form which this question took at the commencement was, How far is the digestion of food in the alimentary tract carried out by bacteria? Some authors even went so far as to suggest that all the katabolic changes in the intestine are due to bacteria, so that, in their absence, life would be impossible.

It is manifest that the difficulties in the way of deciding this question are enormous. One of the earliest attempts at its solution was made by Baumann, who endeavoured to disinfect the intestinal contents of a dog by repeated administration of small doses of corrosive sublimate. As might be expected, his success was partial only; nevertheless, he was able to come to the conclusion that certain of the constituents of the urine are due to putrefactive changes in the intestine. To this source he ascribed the acid sulpho-compounds and the hippuric acid; the aromatic oxy-acids he regarded as being derived from the physiological life of the tissues.

But the only possible way in which the question could satisfactorily be approached was adopted by Nuttall and Thierfelder. These investigators reared guinea-pigs from birth under completely aseptic conditions. At the end of pregnancy they performed aseptic Cæsarian section, received the newly-born animals into a sterile chamber, supplied them with sterile air, fed them upon sterile milk and biscuit, and at the end of the experiment proved the existence of a perfect asepsis by cultural methods. They found that animals can grow under aseptic conditions, though perhaps not so rapidly as under normal conditions; this, however, might fairly be expected to depend, in whole or in large part, upon conditions other than the presence or absence of bacteria. In the urine of the guinea-pigs aromatic oxy-acids were present; these bodies—as was held by Baumann—can therefore be formed independently of putrefaction. On the other hand, phenol, cresol, indol, skatol, and pyrocatechin, substances which are present in the fæces of animals living under ordinary conditions, were completely absent from the fæces of the aseptic guinea-pigs. These substances must therefore be regarded as by-products of proteid putrefaction.

Nevertheless, the question, whether that disintegration of the proteid molecule which is brought about by bacteria in the alimentary canal, is an aid to the economy, is still unanswered. The fact that many infants, who fail to gain weight when fed with sterilised milk, commence to improve directly they are given unsterilised milk, is noteworthy in this connection.

III. **Fragmentation of the Heart.**—Concerning this condition but little is known; it is even doubtful whether it is, or is not, a post-mortem change. The condition shows itself macroscopically by a peculiar friability of the myocardium. The heart wall is thin, pale, friable, and with the back of the knife one can easily scrape from a cut surface a mass which, microscopically, is seen to consist of muscle-cells, red blood-corpuscles, and a little connective tissue. The muscle-cells are very little altered, and apparently the change is essentially one of the connective tissue.

The change was incidentally described by Coats in 1872, and since that time it has received attention from Renaut and Landouzy, Browicz, Tedeschi, and others. It is apparently associated most commonly with cardiac dilatation and failure, and is important in that it is frequently found in cases of sudden death in which no other cause can be inculpated. Thus Tedeschi found that of seven cases of sudden death, none of which showed any other possible cause, six showed fragmentation of the heart; in numerous other cases of sudden death from accident, suicide, and murder, it was very rarely observed. Tedeschi, who is strongly of opinion that the condition is not due to post-mortem change, found it most commonly in cases of infective disease and of acute and chronic disease of the central nervous system. Renaut and Landouzy observed that it occurs particularly in sudden death from cardiac causes, and after acute infective disorders. Besides the conditions mentioned, fragmentation of the heart has been found after death from acute nephritis (Renaut and Landouzy), angina pectoris (Œstreich[1]), after death preceded by a long death agony (Browicz), and after death occurring four days after laparotomy, and perhaps due to after-effects of chloroform-inhalation (Ambrosius).

In spite of numerous attempts on different mammals, Tedeschi was unable to produce the change experimentally, except, perhaps, after he had severed the vagus, and in the neighbourhood of the lesion produced by application of a red-hot needle to the myocardium.

IV. **On Death from Certain Causes.—(i.) Death after Extensive Superficial Burns.**—In cases of burns and scalds, when one-third or more of the body has been involved, death almost always supervenes, even though the skin may have been merely reddened. In this respect there is the greatest contrast between the effects of burns and those of inflammatory infections, such as eczema and other forms of dermatitis, which are by no means necessarily fatal, though they affect an equal, or even a greater, surface.

The constitutional effects of extensive superficial burns and scalds, as determined on lower animals, consist in fall of general blood-pressure and of body temperature, restlessness, superficial and irregular breathing, a tendency to coma, weakness of pulse, together with, perhaps, hæmaturia or hæmoglobinuria, and bloody diarrhœa. The part of the body affected has a marked influence upon the severity of the symptoms produced; for instance, in the rabbit, the constitutional disturbance produced by scalding the ear is much greater than that produced by a scald of the same severity and extent affecting the hind limb. In man the effects of burns and scalds are very similar to those observed in lower animals.

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[1] See p. 82.

Many suggestions have been put forward to explain the peculiarly severe effects of burns and scalds. They may be divided into groups according as the essential cause was supposed to be (1) failure of cutaneous perspiration (Follin), (2) formation of a special poisonous substance in the blood (Billroth), (3) changes in the formed elements of the blood (Max Schultze, Wertheim and Ponfick, Welti, Silbermann, Lesser, Salvioli), (4) reflex nervous changes induced in the heart and blood-vessels (Falk, Sonnenburg, Fischer), (5) inhibition of tissue exchange (Brown-Séquard), (6) shock, which most English authors regard as the real cause of death, and which many foreign authors (*e.g.*, Sonnenburg, Kijanitzin) allow plays a part in bringing about the final result.

Speaking broadly, we may therefore say that death after superficial burns and scalds is by most authors ascribed either to shock, or to a direct poisoning by some substance formed as the result of changes undergone by the tissue- and blood-cells destroyed in the area affected, or to a combination of these two conditions.

With regard to shock, sufficient has already been said in Chapter XI. to indicate that the symptoms of shock and collapse are closely similar to those observed after extensive superficial burns, and there seems no doubt that a very considerable proportion—if not the whole—of the symptoms, including death, are explicable on the assumption that they are due to shock when death supervenes early, to shock and collapse when death supervenes later.

But it is not impossible that some definitely poisonous substance may take a part in inducing the shock and collapse.

Lustgarten likens the symptoms after burns to those seen in poisoning by trimethylamine, muscarin, and other poisons, and thinks they are produced by a "ptomaine." Kijanitzin examined the blood chemically, and asserts that he separated such a ptomaine from the blood of dogs and rabbits that lived a short time after exposure to heat. In the case of less extensive burns and scalds involving the true skin, there can be little doubt that, before granulations have been formed, absorption of toxic substances of bacterial origin—a kind of sapræmia—plays a considerable part in producing the febrile and other symptoms observed; the raw surfaces exude considerable quantities of fluid in which micro-organisms can easily multiply.

(ii.) **Death by Drowning.**—Death by drowning has been investigated on dogs by Brouardel and Loye, and it is chiefly from their papers on the subject that the following statements are taken.

Brouardel and Loye divide the period elapsing between immersion and death—about three and a half minutes—into five phases: (1) the phase of surprise (ten secs.), (2) the phase of arrested respiration (one min.), (3) the phase of deep inspirations (one min.), (4) the second phase of arrested respiration (one min.), (5) the terminal phase, in which there are a few respiratory movements (thirty secs.).

Of these phases the second is of the utmost importance, for though during it there are respiratory movements, *no water enters the lungs.* This does not depend upon closure of the glottis, but is due to immobility of the thorax brought about by reflex stimulation of the mucous membrane of nose, mouth, pharynx, larynx, and trachea by the water. The second phase is further of importance, in that during it syncope may occur. This syncope may be permanent, and therefore fatal, but it probably also explains all cases in which recovery takes place after immersion for more than one minute or a little over. The reason of this is that syncope prolongs the second phase during which water fails to enter the lungs; once water has entered the lungs with inspirations of the third phase, recovery is probably impossible.

The curve given by the general blood-pressure in drowning is practically identical with that seen in asphyxia. Indeed, the general symptoms throughout as to convulsions, state of pupils, insensibility, etc., are closely similar in the two cases. It must be noted, however, (1) that a drowning animal lives about half a minute less than an animal in asphyxia, owing to the fact that during the early phases of drowning, air is expelled from the lungs which contains a certain amount of oxygen, whereas this is not the case when the trachea is obstructed; (2) that, in drowning, breathing is chiefly diaphragmatic, in asphyxia, chiefly costal; (3) that the animal in asphyxia endeavours to obtain the oxygen it needs, the drowning animal endeavours to prevent entry of water into its lungs.

(iii.) **Death from Thirst.**—Death from thirst, unlike death after burns and by drowning, is rarely seen; but it presents certain interesting points from a theoretical point of view. Judging from the fact that in this form of death the fluid which is constantly being given off by the lungs and skin is not replaced, one might expect to find that a condition akin to collapse is produced in which the tissues are dry and of high specific gravity, and the blood is also of high specific gravity and of tarry consistency. So far as the specific gravity of blood and of tissues in death from thirst is concerned, I am not aware that any observations have been made, but stories of shipwreck and of travellers who have been lost in the desert, and the direct experiments of Longet, of Pernice and Scagliosi, and others, leave no doubt as to the thickness of the blood and the dryness of the tissues.

But the symptoms yielded by an animal deprived of water are, in many respects, unlike those of collapse, for he is more likely to become maniacal than comatose—except when he is moribund. Tiedemann, describing the symptoms in travellers lost in the desert, speaks of dryness and burning pain in the throat, loss of voice and difficulty of speaking, rapidity of respiration and of pulse, conjunctival hæmorrhages, burning skin, loss of muscular power and of consciousness, and mania. Pernice and Scagliosi, too, noted the symptoms just mentioned in a dog and three fowls that were deprived of water. After death, they found great congestion of the brain and spinal cord, together with atrophy of ganglion cells, degenerative changes in the medullated nerves, and proliferation of the neuroglia cells. On the whole, their description agrees with that of Longet, who considered that "thirst kills like an inflammatory disease," for in the abdominal organs they found many foci of inflammation and of gangrene besides the thickness of blood and dryness of tissues already mentioned.

An animal deprived of water does not live so long as one deprived of food alone. Thus Succi, the fasting man, lived 40 days without food, but according to Longet an animal deprived of water lives 3–4 days only, according to Birch-Hirschfeld, 6–12 days only. The dog which was the subject of Pernice and Scagliosi's experiment lived 11 days. No doubt the actual length of time before death supervenes in these cases depends largely upon the temperature of the external air.

(iv.) **Death by Lightning.**—Though deaths by lightning are, unfortunately, not very infrequent even in England, little or nothing is known as to the processes whereby death in these cases is brought about. The actual effects of lightning as it passes to earth through the body of a man vary within a very wide range. The individual may be killed outright, and may present neither symptoms nor signs of injury. As a rule, however, the body shows more or less marked signs of the violence with which it has been attacked; these may consist in superficial discolorations or burns, in hæmorrhages, in actual lacerations of the skin and deeper tissues, and such like. Usually the clothes of the individual are torn, and, as in a case which occurred near Guildford, and is reported in the *Lancet*,[1] they may be scattered in shreds around the body for a distance of several yards. The boots, in particular, are liable to suffer, probably because they are in direct contact with the earth; they are often burst open, the soles torn off, and the nails driven out. When the individual's clothes are dry, they offer a greater resistance to passage of the electric current than when they are wet, and the damage which they suffer is proportionately greater. For the same reason, it is probable that if an individual in dry clothes forms the path for an electric discharge, he runs a greater risk of death than if his clothes are wet. Sometimes death by lightning is preceded by profound shock, paralyses, or convulsions.

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[1] September 4, 1897.

Death by electric shock has recently been made the subject of experiment by Oliver and Bolam. These investigators exposed dogs and rabbits to the action of an alternating electric current (varying in potential from 25 to 290 volts) for a period, generally, of two seconds. They found that with a current of, roughly speaking, 100 volts, death is instantaneous, respiration and cardiac action being arrested, the latter perhaps after a temporary quickening. But the important point brought out by the experiments is that, in these cases, death is the result of arrest of cardiac action, and not of respiratory paralysis. The curves given show conclusively that respiration may be resumed after the circuit has been broken, though the heart does not recommence to beat. According to the authors, in the dog, respiration may continue even for "a minute or two" after the heart has ceased to beat, and the animal may bark loudly. Primary arrest of respiration, with subsequent failure of heart, was never observed, though simultaneous arrest of the two functions sometimes occurred in cases where a current of very high potential was used. After death of the animal, it was found that the left ventricle "may contain a very small quantity of blood, while the right ventricle, auricle, and the large veins near the heart are distended with dark fluid blood." Such a condition is exactly what might be expected from the experimental data.

Lewis Jones, who investigated the effects of continuous electrical currents of high potential, obtained (in 1895) results identical, in their essential points, with those of Oliver and Bolam.

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